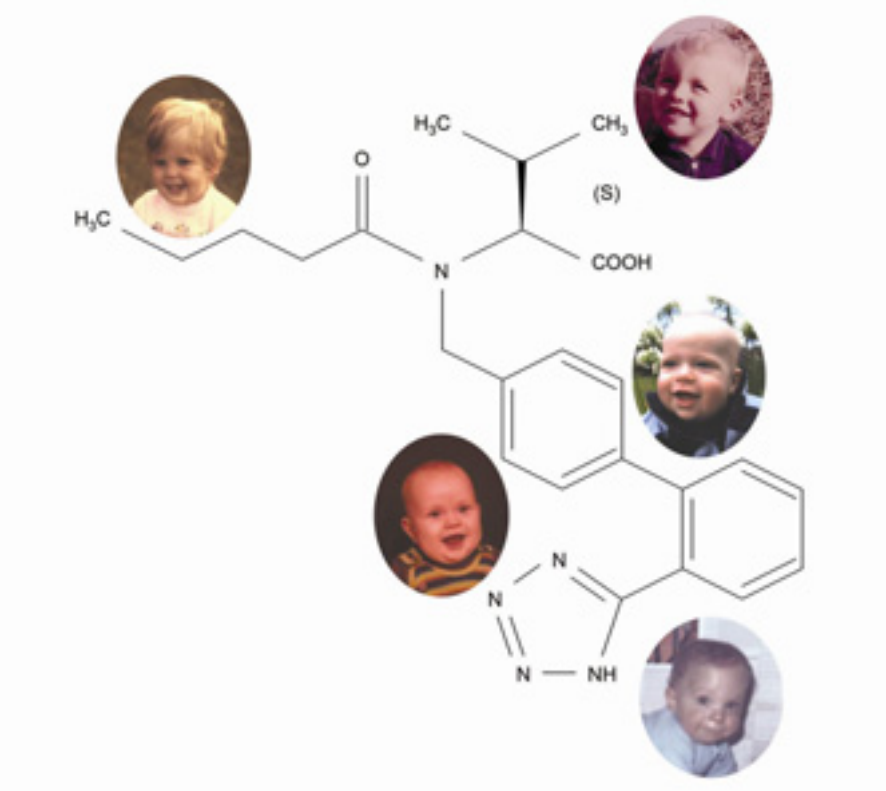
Deutsche Bank

5 August 2005

Global Pharmaceuticals

Pharmaceuticals for Beginners



Primer

Pharmaceuticals for Beginners—Third Edition
The August 2005 publication of 'Pharmaceuticals for Beginners' is the third edition of this industry beginners' guide, which was first published in 2001. Structured in three parts, this comprehensive report includes details on the workings of the industry, key therapeutic markets and a summary of the leading drug companies.

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DISCLOSURES AND ANALYST CERTIFICATIONS ARE LOCATED IN APPENDIX 1

Deutsche Bank

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So, you've inherited the pharmaceutical sector. Big companies, loads of market cap and interesting diseases with some very silly names. Fantastic – finally you've got to follow a stock market industry that might actually be of some interest to that person sitting next to you at a dinner party.

But wait. Why do all these drugs have at least two names and how do they work? What is a COX 2 inhibitor and why can't analysts just say heart attack or acid stomach instead of using lengthy terms like myocardial infarction or gastro-esophageal reflux disorder? And what on earth is a randomised, placebo-controlled, double blind, intention to treat, Phase III clinical trial anyway? Oh no, what have I done?!

In our view, the pharmaceutical industry is fascinating, exciting and of obvious relevance beyond the stock market. But it is also very technical and comprises a minefield of products, names and pathways. Keeping track of it all can, at times, prove bewildering, and not just for the uninitiated.

With this in mind, in January 2001, the global pharmaceutical team at Deutsche Bank first published a document that we hoped would prove of use for beginners and industry old hands alike – Pharmaceuticals for Beginners. Such a success the first edition was that we are now on our third edition in which we have further updated and expanded our original text. As in the past, the report is structured in three parts providing insight into industry basics, therapeutic markets and the world's leading pharmaceutical companies. The current edition covers some 25-disease areas, including an expanded oncology section as this therapeutic area has been one of the most rapidly evolving in recent years. We have also included a new section on the US litigation process (key for following patent lawsuits) as well as an expanded discussion on Medicare and the new prescription drug benefit.

Pharmaceuticals for Beginners is not intended to be read cover to cover, but is meant as an easy-to-use reference guide. Although our concept was to provide beginners with an easy-to-comprehend insight into an undoubtedly complex industry, we hope that it will also continue to find favour among more learned readers as well. Overall, we trust that our readers will find it a valuable and useful document and entrust it with a permanent slot on an already overcrowded desk.

So, for those who want to know exactly what a dual PPAR agonist is, turn to the therapeutic comments on diabetes, or to understand why VEGF inhibitors have been gaining so much attention, turn to the oncology section. We wish you a happy and informative read.

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Innovation: The key to growth

Mankind's drive to defeat illness and disease and improve quality of life has made the pharmaceutical industry one of the largest and most significant global businesses. Driven by its own ability to innovate, the industry has grown strongly over the decades, as successful new medicines have extended average life expectancy and as governments across the globe have sought to improve the health and quality of life of their citizens. Following many years of consistent and steady growth, today's global pharmaceutical market is estimated to be worth $500bn. With science continuing to innovate, new and exciting developments over the coming years, not least from unravelling of the human genome (our own book of life), can be expected to drive further strong growth in the years ahead.

Our pharmacopoeia surrounds only 500 drug targets

Today, people are living longer, healthier and more productive lives as a result, in considerable part, of the efforts of the research-based pharmaceutical and biotechnology industries in discovering new medicines to prevent, cure and treat disease. Starting with the discovery of vaccines and the later development of the antibiotic industry, illnesses that at the start of the twentieth century were often fatal - such as polio, smallpox, syphilis and consumption (tuberculosis) - have today either been eradicated or have effective treatments. Advances in molecular biology and our understanding of the body's chemistry have enabled us to develop drugs that help our hearts pump longer, our lungs breathe more freely and our minds act more clearly. And yet, amazingly, we are only at the beginning. Today, our entire universe of drug receptor targets and, with it the basis of much of today's industry, only extends as far as 500 or so distinct sites for drug intervention. As the mysteries of the human genome are deciphered, this figure is expected to advance between six- and 20-fold to nearer 3,000-10,000 within our lifetimes. Of itself, this suggests the potential for explosive industry growth.

Genomics and rational drug design hold great promise

As we enter the twenty-first century and our understanding of the human body further improves, drug discovery is moving away from its earlier serendipity and becoming ever more rational and industrial. Advances in chemistry mean that we can now design molecules that will react with a particular body protein and test them rapidly and repeatedly with the use of complicated laboratory machinery. Gone are the days of little men in white lab coats, pipette in hand, test tube in rack and bunsen burner on the laboratory table. Equally, advances in information technology and computer software, together with the Internet, have allowed us to predict and visualise the interactions of a drug with the chemistry of the body. Tests can now be conducted with accuracy *in silico,* while information and new discoveries can be transferred to a global audience in a matter of minutes. As a consequence, the structure of the industry is changing and will continue to do so. For the corporations involved, critical mass is increasing as the business of research increases in cost and the need to recover that cost drives an ever-growing need to penetrate end-markets and disseminate product information. Despite a decade of mergers, the research-driven industry remains highly fragmented, the largest player controlling no more than 11% of total industry sales. Research productivity shows few signs of improvement, while critical mass continues to increase. Growth there may be, but, as the cost of discovering, developing and launching drugs continues to escalate and governments strive to contain the health care burden associated with an ageing population, industry structure will, in our opinion, continue to alter.

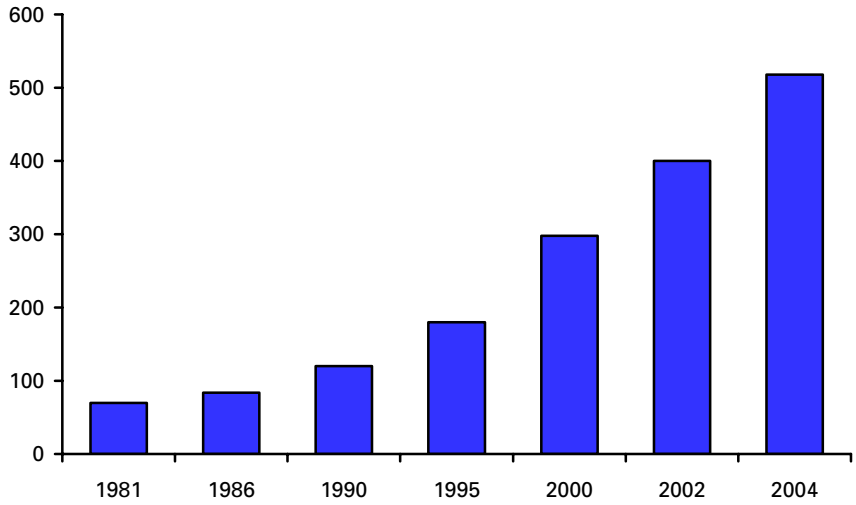
Overview

A $500bn industry

In 2004, pharmaceutical industry revenues from prescription drugs totalled over $500bn. From a value of nearer $70bn in 1981, the industry has recorded compound annual revenue growth of just under 10% and, despite today's much greater size, it is of note that underlying volume growth rates have seen little sign of abatement over the 20-year period. Geographically, the US has grown in importance and today accounts for roughly 50% of total industry sales. US revenues have gained not only from a more favourable pricing environment but also from the growth of biotech-derived products and the market stimulus provided by direct-to-consumer advertising. Freedom of choice in US healthcare markets, combined with market-based pricing, argue that US growth will continue to outpace that of the other major world markets and that the US will continue to increase in importance overall.

By contrast, government-influenced buying and formulary control have meant that the importance of European revenues as a percentage of the total industry has declined over the past 20 years. Today, Europe accounts for less than 30% of global revenues. Equally, the Japanese government's influence in domestic pharmaceutical markets has restricted the rate of absolute sales growth, with Japanese end-markets today accounting for 11% of total industry sales.

Figure 1: Value of the pharmaceutical industry 1981-2004 ($ bn)

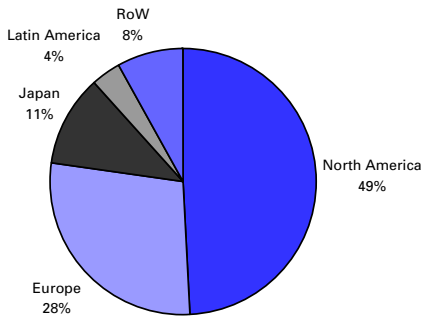


Source: IMS Health, Deutsche Bank estimates

Cardiovascular and CNS drugs dominate

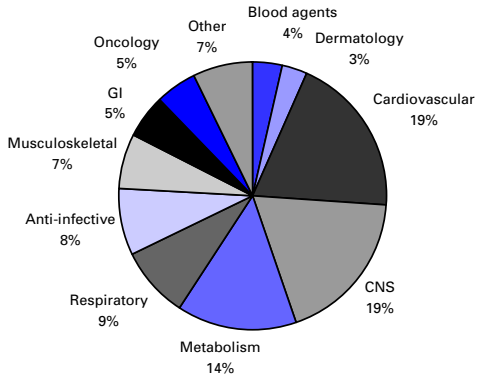
By therapeutic category, today's industry is dominated by demand for cardiovascular drugs (including the cholesterol-lowering agents), which, in 2004, were estimated to account for nearly 20% of industry sales, or around $90bn by value. Pharmaceuticals for disorders of the central nervous system – an area that remains poorly understood in medical terms – represent the second-largest category, driven in recent years by the emergence of important drugs for treating mental illnesses such as depression and schizophrenia. Anti-infectives, predominantly antibiotics, retain their importance as a major therapeutic class, despite the age of many of the key products. In 2004, we estimate that anti-infectives represented 8% of global pharmaceutical sales. Elsewhere, strong growth in genito-urinary treatments, most significantly those for ulcers and acid reflux, has enabled them to retain a 5% share of global markets, while the growing prevalence of respiratory diseases such as asthma in the industrialised world, has seen this category retain its 9% share.

Figure 2: 2004 drug sales by region



Source: IMS Health, Deutsche Bank

Figure 3: 2004 drug sales by therapy



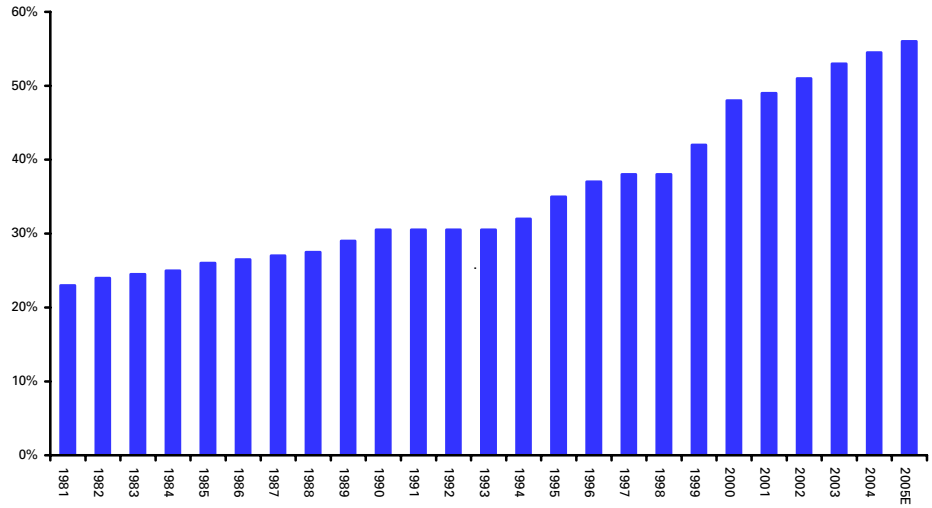
Source: IMS Health, Deutsche Bank

Consolidating, but still fragmented

From a company perspective, innovation and consolidation have meant that an increasing proportion of global sales are concentrated in the hands of the top ten players. This process has accelerated in recent years, following the mega-mergers of companies like Glaxo Wellcome with SmithKline Beecham and Sanofi-Synthelabo with Aventis (where all four of the legacy companies were themselves created by mergers within the past ten years), Pfizer with Warner-Lambert and, shortly afterwards, Pfizer with Pharmacia. The ongoing process of focus by the world's chemical industries has also seen companies such as DuPont and BASF reconsider their ambitions in what were historically core markets, BASF selling its Knoll business to Abbott and DuPont its pharmaceutical assets to Bristol-Myers. We estimate that the top ten ethical pharmaceutical companies accounted for around 55% of industry revenues in 2004, against 25% two decades earlier. However, despite this consolidation, it is of significance that the world's largest company, Pfizer, still accounts for only 11% of industry revenues. In part, this pays testament to the sustained innovation evident in the industry and the fact that, despite its absolute scale, markets are not mature and growth comfortably in excess of world GDP is still, in our view, achievable.

Individual drugs, too, have become larger, with the top ten today accounting for around 10% of total industry revenues, against just 5% two decades ago. In 2004, 82 drugs achieved $1bn blockbuster status, with the world's largest drug, the cholesterol-lowering Lipitor, realising sales in excess of $10bn.

Figure 4: The market shares of the top ten companies 1981-2005E



Source: Company data, Deutsche Bank estimates

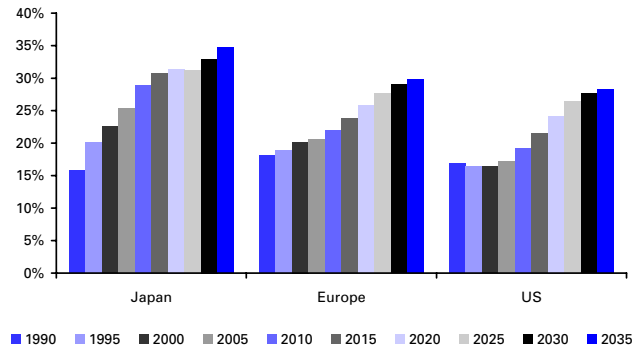
Growth, but not without its pressures

Demographics and innovation strong drivers

In large part, the significant growth of the pharmaceutical industry reflects the new discoveries and medicines that the industry has developed and the impact that these have had on life expectancy. Given that the elderly tend to account for the greatest proportion of drug usage (see Figure 6), the older the population, the greater the demand for drugs. However, beyond research innovation and the greying of the population, industrialisation of the developing economies and a greater emphasis on market penetration, including the use of direct-to-consumer techniques, have all helped fuel growth. Equally, improvements in drug regulatory approval times over the past ten years have facilitated growth by affording patented drugs a greater period of market exclusivity (albeit the increased length of the clinical trial process has to date eaten into much of this benefit).

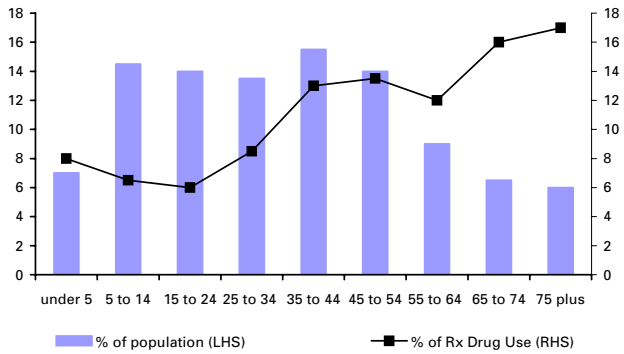
- **Demographics**: Populations are not getting any younger, particularly in the world's developed economies. Indeed, it is estimated that every five years since 1965, roughly one additional year has been added to life expectancy at birth. In the US, life expectancy at birth in 1920 was a modest 54 years. By 1965 it stood at 70 years, while today, the average life expectancy at birth stands at 77 years. The importance of these statistics is that as we get older, we consume more medicines. Indeed, industry bodies estimate that healthcare expenditures for people aged 65 and older are nearly four times those of people under 65. Looking ahead, we expect the population of the developed world to continue to live longer. The absolute number of elderly people will also increase as the baby-boomers turn 65 from 2010 onwards. Overall, the next 50 years are expected to see a doubling of the number of Americans aged 65 or older.

Figure 5: Estimated % of regional populations over 60 from 1990-2035E



Source: World Bank

Figure 6: US prescription use by age and population by age

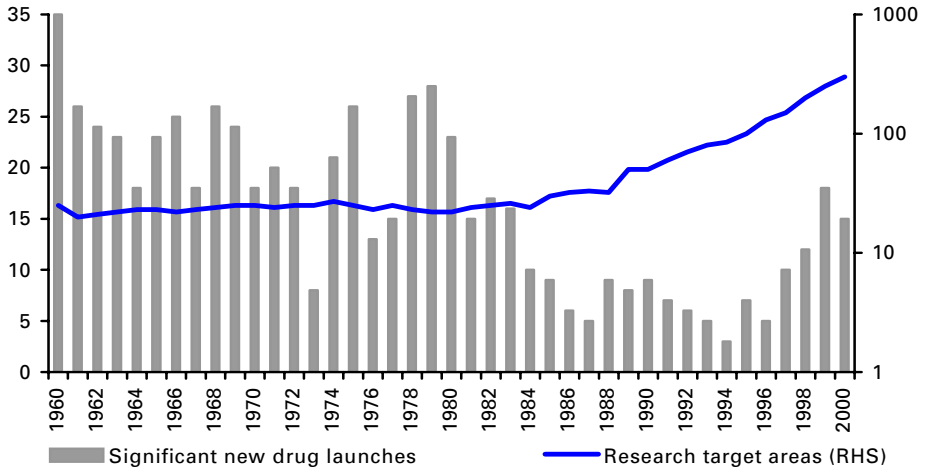


Source: National Ambulatory Medical Care Survey

- **Innovation:** As the industry has grown, it has invested more and more money in research and development in search of new medicines to better treat disease. In the US alone, the industry trade body PhRMA (Pharmaceutical Research and Manufacturers of America) estimates that pharmaceutical R&D spending in the US has increased more than tenfold over the past twenty years. As a consequence, more molecules than ever before are entering research pipelines (although failure rates are also rising, as we shall discuss later). In part, this increase has been fuelled by a strong increase in the absolute number of new targets for drug interaction, from around 100 at the start of the 1990s to

nearer 500 today. However, as we enter the era of genomics and our understanding of our genes and the proteins they encode improves, that number is expected to increase between six- and 20-fold. Such an increase in targets, and with it, understanding of the body's chemistry, must be expected to drive a substantial increase in our ability to develop new medicines to treat and prevent disease.

Figure 7: The number of drug receptor targets is increasing rapidly



Source: Company data, Deutsche Bank estimates

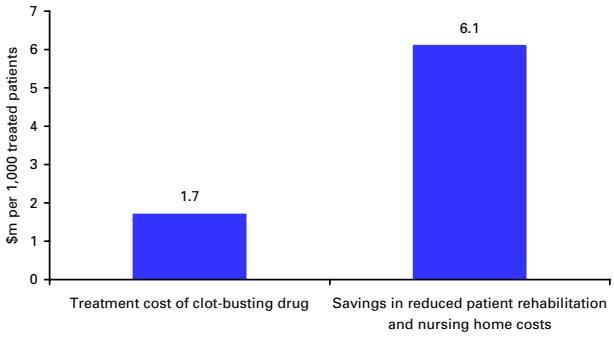
- **Market penetration:** Outside new drug development, the pharmaceutical industry has become better at marketing its own products and seeking additional opportunities for a drug's use. Companies have learnt that to maximise the value of medicines that are increasingly costly to develop, they need to penetrate markets more rapidly and more broadly. The result has been a surge in the number of representatives used to sell new and existing pharmaceuticals. In addition, companies are seeking as many medical indications for their drugs as possible. Thus, if a drug that was initially developed for depression has a beneficial impact on sufferers of pre-menstrual tension, the drug company itself will undertake clinical studies to demonstrate the product's efficacy against this previously untapped market opportunity. In part, it is this drive to maximise the range of disorders for which a single drug may show clinical benefit that has spurred the development of an increasing number of drugs that generate revenues in excess of $1bn. Thus, whereas in 1990, only seven pharmaceuticals realised sales in excess of $1bn, by 2004 this number stood at 82.

  Beyond seeking an increase in the number of indications for which any one pharmaceutical may be prescribed, the advent of direct-to-consumer advertising in the US has also helped spur growth, by allowing the industry to increase patient awareness of available treatments for disease. Markets are increasingly consumer driven, aided not least by the Internet and, with greater awareness of choice, lifestyle drugs have come of age. Thus, while addressing a serious medical ailment, products such as Pfizer's Viagra for impotence, Merck's Propecia for hair loss and Allergan's Botox for brow furrow all hold the potential to attain far greater sales and market penetration than might have been the case but ten years ago.

- **Industrialisation:** As the GDP per capita of the developing nations improves, so the ability of those governments and their population to afford new medicines increases. The populace's expectations for health care also increase. Today, emerging markets such as those in the Far East and Latin America represent important sources of revenue for the global industry as a whole.

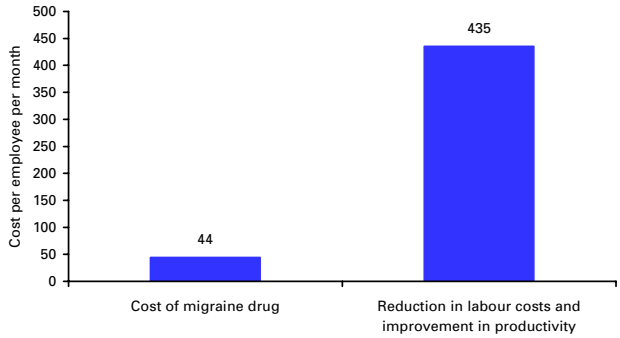
- **Healthcare budgets:** Finally, it is also worth stating that relative to hospitalisation, surgery and lost productivity, pharmaceuticals represent a very cost-effective means for governments or insurance companies to contain the healthcare costs of an ageing population. Of course, the profitability of the industry makes it an easy target for government to attack as it seeks to hold back the steadily rising costs of providing a healthcare system. However, the reality is that the use of pharmaceuticals saves society huge costs every year in the management of disease. As such, simple economics dictate that healthcare authorities around the world must ultimately drive an increase in their use if aggregate cost containment is to be achieved.

Figure 8: Cost vs. savings for anti-thrombotic ($m)



Source: Fagan FC et al (1998)

Figure 9: Cost vs. savings for migraine drug ($)



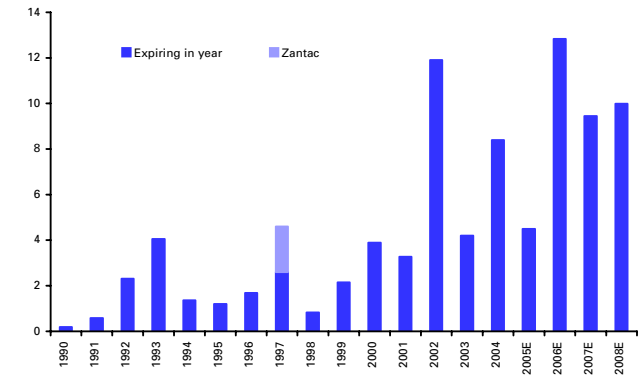
Source: Legg RF et al (1997)

Industry pressures increase

We have already argued that the pharmaceutical industry holds the potential for continued robust growth into the medium term and beyond. Yet it also needs to be recognised that there are major cost and revenue pressures facing the industry and that these are likely to impact on revenue and profit growth over the next few years. Not least among these are the increasing costs of clinical and pre-clinical research, pressure on pharmaceutical prices, the increased costs of marketing and sales, greater intensity of competition in therapeutic classes and, very notably over the next five years, the threat of patent expiries. It also must be stated that these pressures are arising at a time when drug pipelines look relatively thin and R&D productivity would appear to be faltering.

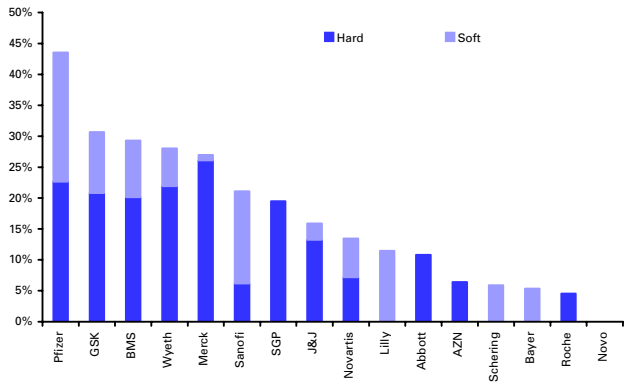
- **Patents.** The past few years have highlighted the pressures exerted upon pharmaceutical company profits following the patent expiry on a best-selling product. Patent expiries totalling almost $12bn in 2002 saw several companies including Bristol-Myers, Eli Lilly, GSK, Merck and Schering-Plough announce a reduction in earnings expectations as they grappled with the negative profit impact of patent expiries on one or more best-selling products. Although 2005 looks likely to see a moderation in the value of revenues lost to generics (excluding 'soft' patent expiries, or those where the patent is currently being litigated in the courts), the deleterious effect of patent expiries looks set to remain an important theme into the medium term, as a fistful of significant products lose patent protection over the next few years. At a time when few companies are able to boast a late-stage pipeline that holds anything of much interest, revenue growth for several of the leading drug companies is likely to come under considerable pressure.

Figure 10: Revenues lost to US patent expiry 1990-2008E ($ bn)



Source: Company data, Deutsche Bank estimates

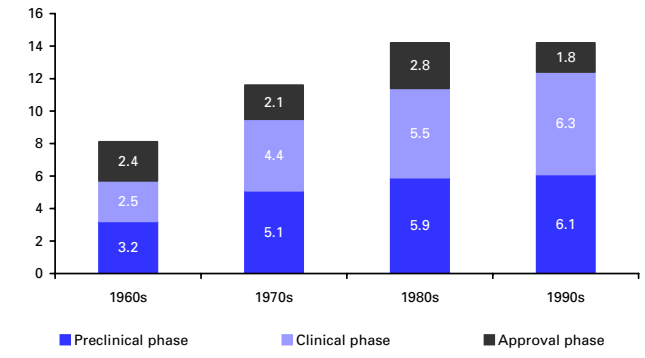
Figure 11: US exposure by company 2004-2008E (% 2004 sales)



Source: Company data, Deutsche Bank estimates

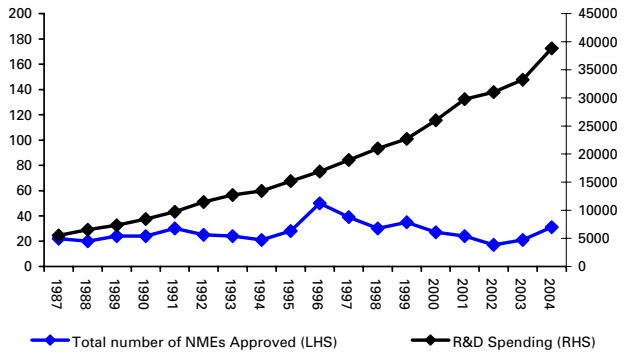
- **Research costs:** We have stated that the genomics revolution holds important potential for industry growth and the development of new pharmaceuticals later in the decade. In the interim, however, establishing the technology platforms to maximise the potential of these new technologies represents a major and unavoidable up-front investment. In addition, while technology breakthroughs are industrialising the research process, the time taken to get products to market, together with the cost of developing new chemical entities continues to rise. As illustrated by Figure 12, it is estimated that the average time taken to get a product to market has increased over the past 20 years to almost 15 years – a near 20% increase. On average, almost 70 clinical trials are now undertaken for each new drug application, compared to nearer 30 at the start of the 1980s, with each new drug application today requiring over 4,200 patients compared to just over 1,300 20 years ago.

Figure 12: Time to get a new drug to market



Source: Deutsche Bank

Figure 13: R&D spend vs. drugs approved

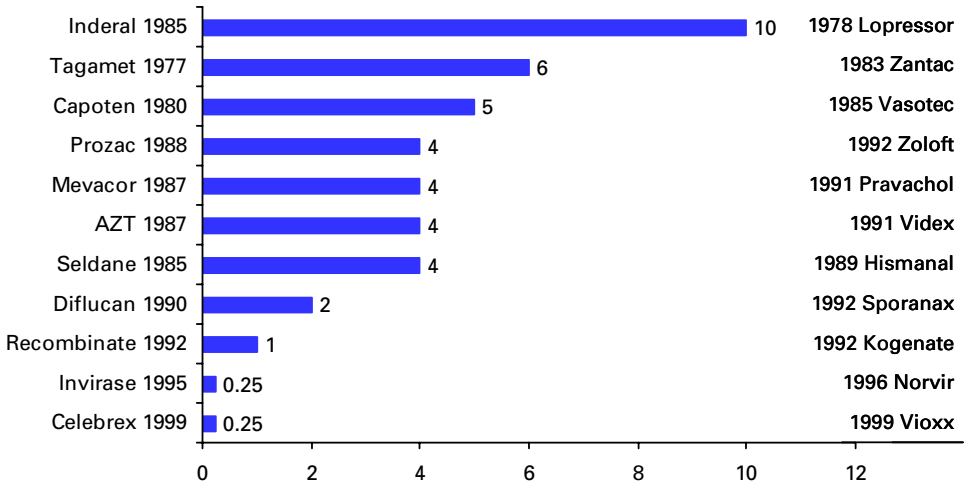


Source: Deutsche Bank

Not surprisingly, this has led to a stark increase in the average costs incurred to develop a new drug. Industry consultants estimate that the average successful drug now costs $897m pre-tax to bring to market, a sum that includes an estimated $150-200m for the cost of drugs that fail to navigate the research process successfully. Put simply, the number of new chemical entities approved each year is in no way keeping pace with increases in the level of R&D spending.

- **Market exclusivity in new classes shortening:** Another feature of today's market is that competition among drugs is increasing. Competitor drugs addressing the same medical condition are entering the market at ever-faster rates. Thus, where six years separated the launch of the ulcer drug Tagamet and its follower drug Zantac, only six months separated the launch of the first COX2 inhibitor, Celebrex, and the second to market, Vioxx. Today, innovator companies have much less time to maximise the potential of their innovation before competition emerges.

Figure 14: Years separating first in class from first imitator



Source: PhRMA, The Wilkerson Group

- **Government and pricing:** With the exception of the US, pharmaceutical prices are predominantly determined by government-controlled authorities. The significance of healthcare costs as a percentage of GDP in most mature economies means that governments are under increasing pressure to control medical costs tightly. Thus, prices are under regular review, with price cuts enforced in many important territories, perhaps most notably Japan (see below). In addition, in several markets, high-priced pharmaceuticals will not be incorporated into national lists, which detail those drugs that may be prescribed by doctors and health authorities (i.e. national formularies). Thus, while an ageing society will result in growth in demand for drugs, the cost pressures on society will inevitably mean that governments have to bear down on price. The alternative is, quite simply, that the costs of healthcare will grow to an unaffordable level of GDP.

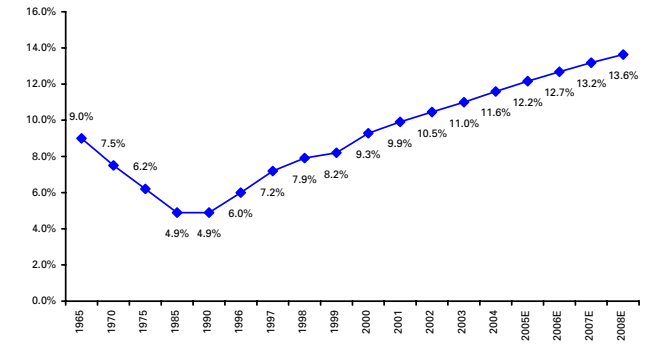
Figure 15: Japan – ongoing price cuts (%)

	1988	1990	1992	1994	1996	1997	1998	2000	2002	2004
Price cut	-10.2	-9.2	-8.1	-7.2	-8.5	-4.4	-9.7	-11	-6.3	-4.3

Source: Ministry of Health & Welfare

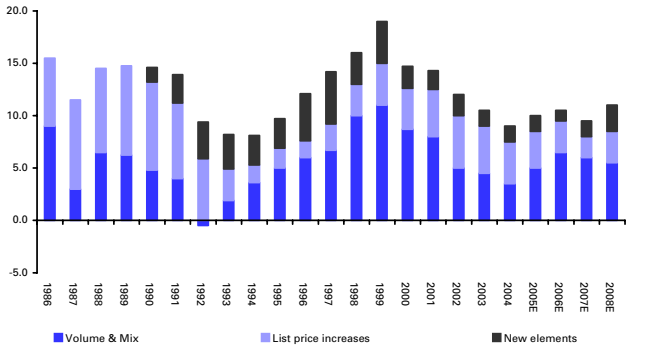
Even in the US, the high relative cost of US drugs and the increasing costs of medical insurance are exerting strong pressure on the industry to contain pricing. Political pressure for some containment of drug prices and industry profitability has also intensified in recent years, not least as the proportion of the healthcare budget spent on drugs has risen at a significantly faster rate than healthcare expenditures overall. The lack of a national health insurance programme, and until recently the lack of prescription coverage for many elderly covered under the federal Medicare programme, has led to considerable political comment on the high price of medicines, together with many initiatives to curb growth in pharmaceutical prices. Initiatives within the private sector that look to push an increasing percentage of the overall drug cost onto the consumer (the so-called co-pay) are also having their effect on market growth.

Figure 16: % of US healthcare spending attributable to prescription drugs



Source: CMS

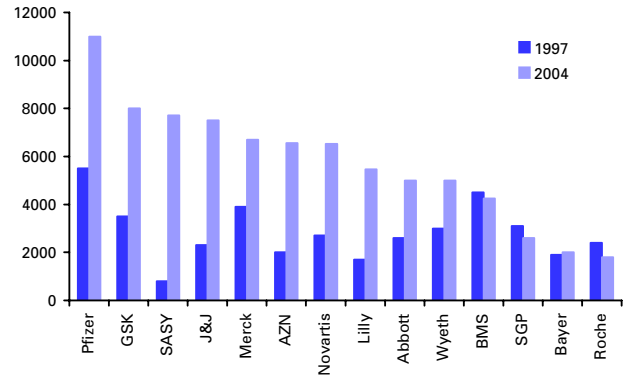
Figure 17: US market growth analysed between price, volume and new drugs



Source: IMS Health

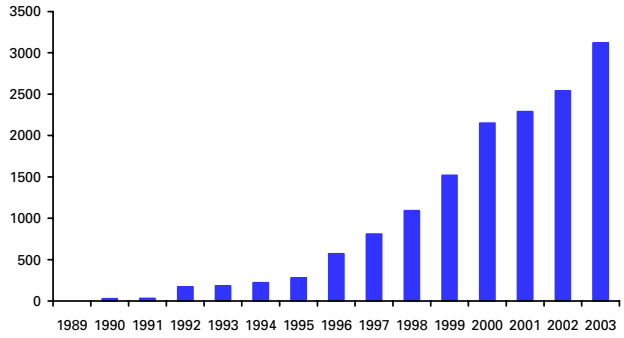
- **Marketing costs:** As companies have recognised the importance of penetrating markets more quickly and achieving peak sales rapidly, so their investment in sales forces and marketing has risen dramatically. Over the past five years, we estimate that the top ten companies have between them invested in an additional 35,000 US sales representatives, taking the total number of reps from around 30,000 in 1997 to nearer 65,000 today. This clearly signifies a huge investment. In addition, companies have spent very heavily on promoting their products using DTC advertising. Indeed, since advertising on television in the US was deregulated seven years ago, DTC spending had risen six-fold to over $3.2bn by 2003.

Figure 18: US sales force numbers 1997 and 2004



Source: Company information

Figure 19: DTC spending in the US ($m)

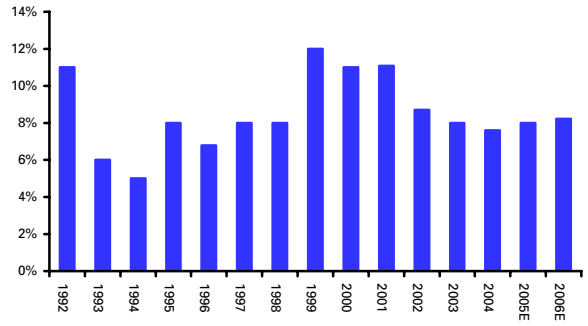


Source: Nielson

Growth, but not without its pressures

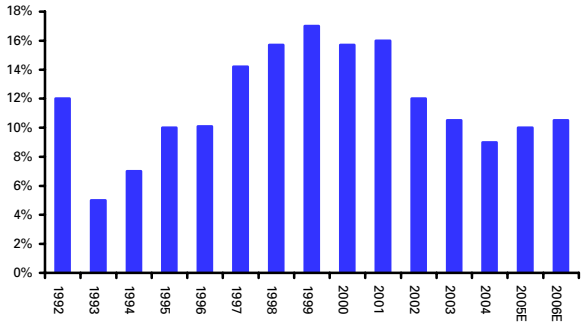
Thus, we can see that while innovation should continue to lead to an improvement in life expectancy and, with it, increasing demand for medication, the industry faces considerable challenges. Growth should, we believe, remain well above that of global GDP, driven significantly by developments in the US market. However, the aforementioned pressures suggest that over the next five years, we must anticipate a slowdown in the pace of growth. As such, it is our opinion that global growth will slow from the 10% or so experienced through 1999 and 2000 to nearer 7-8% by 2002, averaging high single/low double-digit rates thereafter.

Figure 20: World drug growth rates (%)



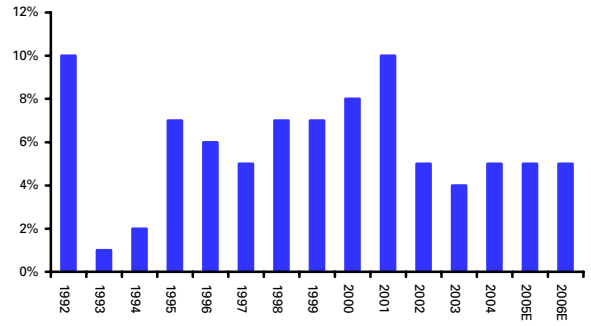
Source: IMS Health, Deutsche Bank estimates

Figure 21: US drug growth rates (%)



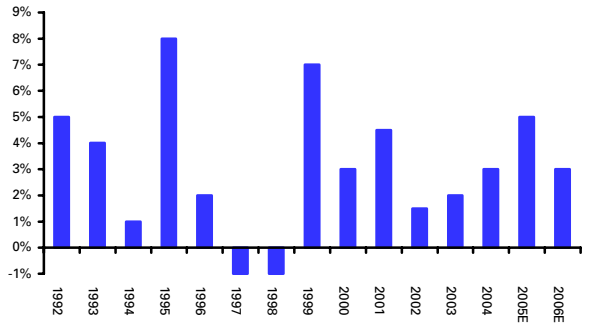
Source: IMS Health, Deutsche Bank estimates

Figure 22: European drug growth rates (%)



Source: IMS Health, Deutsche Bank estimates

Figure 23: Japanese drug growth rates (%)



Source: IMS Health, Deutsche Bank estimates

More consolidation inevitable

For the industry majors, the consequence of these opposing dynamics is that the critical mass necessary to stay in the game, be it R&D or marketing, is rising. Because this is a science- and discovery-based industry, serendipity will no doubt continue to play its role. However, strength in marketing and putting in place the right research platform with strong alliances across the necessary disciplines is becoming ever more important. With so many best-selling drugs also expected to face generic competition over the coming years, the pressures for several companies to remove costs from their business as they seek to retain competitive strength in light of faltering revenue growth is also likely to intensify. All told, the consolidation of the past decade looks unlikely to abate.

The companies

The US and European names dominate

From a corporate perspective, one glance at the leading 20 companies by revenues demonstrates that, despite the significance of the Japanese market to world drug sales, it is the US and European companies that dominate today's industry. Of the top 20 companies by 2001 revenues, eight were European and nine US based. Only three are Japanese, with the largest of these, Takeda, only registering as the thirteenth largest company overall.

Comparison of the league positions in 1981 and those in 2004 does, however, help illustrate the extent to which mergers and acquisitions have shaped the industry over the past 20 years. We estimate that of today's top ten companies, only two – Merck and Eli Lilly – have retained their industry position as a consequence of organic development rather than through acquisition or merger. All other companies have been involved in some major form of M&A activity, a feature that is most apparent among the Europeans, which, with the exception of Bayer and Boehringer Ingelheim, have all merged or acquired over the past five years. It is of note, however, that in essence, today's ten leading companies are the same as those that led the tables in 1981. Only AstraZeneca, Bristol-Myers Squibb, Johnson & Johnson and Abbott are top-ten newcomers.

Figure 24: The 20 leading drug companies with sales and shares in 1981 and 2004

	----- 1981 -----			----- 2004 -----		
	Name	**Sales ($ m)**	**Market Share (%)**	**Name**	**Sales ($ m)**	**Market Share (%)**
1	Hoechst	2,559	3.7	Pfizer	46133	10.5
2	Ciba-Geigy	2,103	3.0	Sanofi-Aventis*	31518	7.2
3	Merck & Co.	2,060	2.9	GlaxoSmithKline	31419	7.2
4	Roche	1,480	2.1	Merck & Co	22939	5.2
5	Pfizer	1,454	2.1	Johnson & Johnson	22128	5.0
6	Wyeth	1,424	2.1	AstraZeneca	20866	4.7
7	Sandoz	1,418	2.1	Novartis	18497	4.2
8	Eli Lilly	1,356	1.9	Roche	17481	4.0
9	Bayer	1,225	1.8	Bristol-Myers Squibb	15482	3.5
10	SmithKline Beckman	1,220	1.7	Abbott Laboratories	13270	3.0
11	Boehringer Ingelheim	1,100	1.6	Eli Lilly	13059	3.0
12	Takeda	1,082	1.6	Wyeth	13021	3.0
13	Upjohn	1,042	1.5	Takeda	10286	2.3
14	Johnson & Johnson	1,008	1.4	Amgen	9977	2.3
15	Bristol-Myers	1,000	1.4	Boehringer Ingelhiem	9419	2.1
16	Schering-Plough	871	1.2	Daiichi Sankyo*	8436	1.9
17	Sankyo	868	1.2	Astellas*	7872	1.8
18	Rhone-Poulenc	825	1.2	Schering-Plough	6417	1.5
19	Shionogi	800	1.1	Bayer	5359	1.2
20	Glaxo	784	1.1	Novo Nordisk	4854	1.1

*Source: Company information, Deutsche Bank *Proforma*

Some strong underlying performances

That said, the M&A activity of recent years also belies some very strong underlying performances and, indeed, some that have been less inspiring. Thus, while the merger of Glaxo Wellcome with SmithKline Beecham afforded those companies a leg up, the enlarged group's underlying market share has also benefited from the strong organic growth of their drug portfolios, broadly doubling over the 20-year period. Similarly, the combination of ICI's

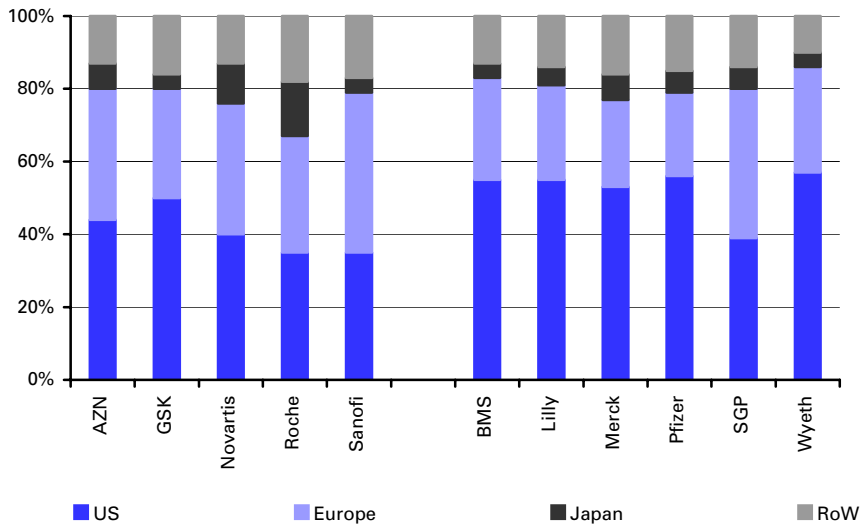
former pharmaceutical business, Zeneca, with the Swedish company, Astra, created a business that in 1981 would have had little more than 1% of the global market. By contrast, in 1981, the combined market share of Ciba and Sandoz (which today comprise Novartis) was over 5%, ahead of market share today. In large part, the failure of the large Continental European companies to retain global market share reflects the lower growth achieved in European markets and, with it, those companies' dependence upon Europe as a source of growth. Greater emphasis on the US market means, however, that this bias is now changing.

Factors driving consolidation

So what has driven this M&A activity? In essence, the reasons are not dissimilar to those in many other industries, with the exception, perhaps, of the threat that the impending patent expiry of a large product can have on a company's future growth potential. Overall, we would indicate the following as the main drivers of consolidation in recent years.

- **Patent expiry**: As stated, the threat of losing patent protection on a drug that represents a significant proportion of sales can have a dramatic impact on profitability and, with it, a company's future. As such, mergers afford the opportunity to cut costs and so compensate for income lost following patent expiry, but also to spread the revenue shortfall over a wider revenue base. Mergers that have been undertaken with patent expiry in mind include Glaxo's 1995 acquisition of Wellcome (Zantac expiry), Astra's 1998 merger with Zeneca (Losec and Zestril expiries), Pharmacia's 1995 merger with Upjohn (Halcion and Xanax expiries), and most recently Sanofi's merger with Aventis (Ambien and Eloxatin expiries and a patent challenge to Plavix).
- **R&D costs**: As the costs of discovering and bringing new drugs to market have increased, so too have the risks of failure and the need to have sufficient mass within R&D to fund growth. In addition, more recently, the breadth of competencies needed to stay abreast of the latest developments in research has led to a burgeoning of expenditure. Critical mass in R&D is now moving well beyond the level of $1bn per annum. Mergers afford a sensible approach to attaining that mass.
- **Marketing mass:** As with R&D, the costs of bringing a product to market are also rising. Sales force sizes, most significantly in the US, are rising, while expensive DTC advertising is a growing necessity. Companies that find they are under-represented in the US market are likely to find that their rate of sales growth is unable to keep up with that of the industry as a whole. US marketing resources and presence were certainly an important feature of the mergers between Ciba and Sandoz in 1996 and Rhone-Poulenc and Hoechst in 1999.
- **Buyer concentration:** Government is never an attractive buyer. It tends to set its own rules. Increased government involvement in the purchase of a drug, most notably in the US, combined with the concentration of buyer power among fewer private health maintenance organisations, have placed downward pressure on achieved drug prices.
- **Geographic expansion:** As the cost of developing drugs has increased, so has the need to realise greater sales of those drugs. In effect, companies need to have the infrastructure in place to distribute and market globally. Where businesses offer a complementary fit, considerable benefits can be derived.
- **Pipeline weakness:** Failure of the R&D effort to consistently develop new drugs with significant potential over a sustained period will almost certainly diminish revenue growth. For example, Bayer's status as a top-ten player has been undermined over the past two decades as little of significance has emerged from the pipeline. Weak pipelines and with them prospects for growth can be overcome through merger activity.

Figure 25: Sales by region for the leading drug companies 2004 (%)

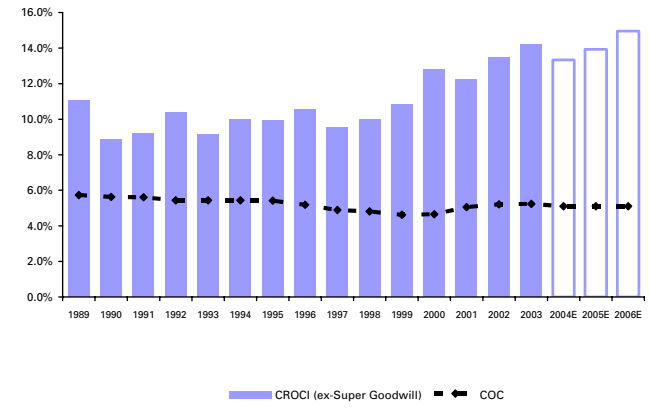


Source: Company data

Europeans less profitable than their US counterparts

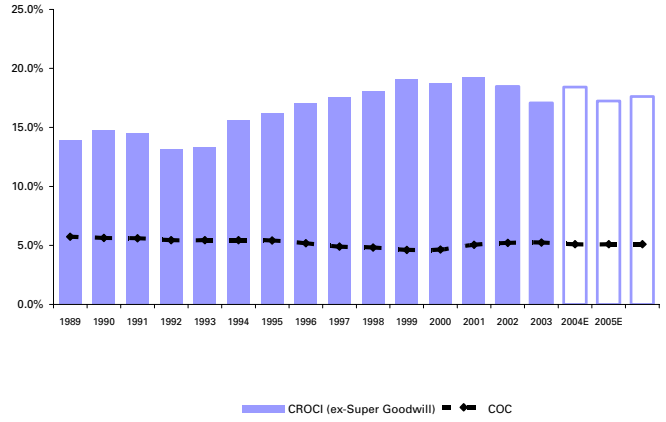
The propensity of the European companies to merge can also be explained by a simple analysis of the returns and growth rates that these businesses have achieved relative to their US cousins over the past ten years. Indeed, if we look at corporate activity over this period, we find that while each of the leading European companies has been involved in a merger, only two of the US majors have taken part in an M&A deal of major significance, namely, Pfizer and Wyeth. The European portfolio approach to business has not paid dividends, nor has the companies' tendency to rely on lower-growth European markets for revenues. Thus, it should come as little surprise that the Europeans have over the past few years been shedding their non-pharmaceutical baggage and emphasising the importance of the faster-growing and more profitable US market for future revenue growth.

Figure 26: European return on capital 1989-2006E



Source: Company data, Deutsche Bank estimates

Figure 27: US return on capital 1989-2006E



Source: Company data, Deutsche Bank estimates

The face of M&A is changing

These are some of the key drivers of merger activity. In addition, the mega-mergers of late, most significantly those of Pfizer and Pharmacia, Glaxo Wellcome and SmithKline Beecham, and Sanofi and Aventis, have upped the ante, reflecting a greater desire to gain competitive advantage from absolute scale.

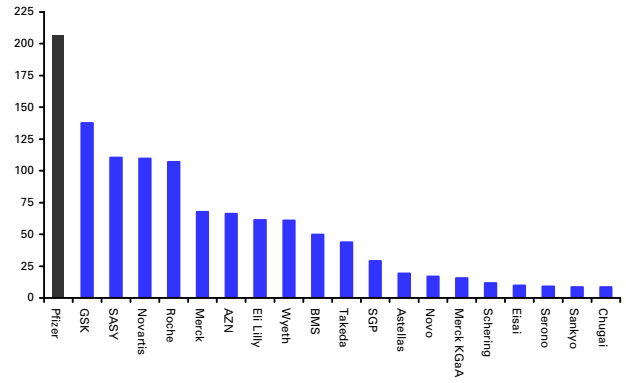
Figure 28: Summary of major industry transactions 1991-2005

Year	Purchaser	Target	Cost of target ($)
2005*	Sankyo	Daiichi	7.7
2005*	Dainippon	Sumitomo	2.1
2005	Yamanouchi	Fujisawa	6.9
2004	Sanofi-Synthelabo	Aventis	72.7
2004	UCB	Celltech	2.4
2003	Pfizer	Pharmacia	64.3
2002	Amgen	Immunex	17.6
2001	Bristol-Myers	DuPont Pharma	7.8
2000	Johnson & Johnson	Alza	11.7
2000	Shire	Biochem Pharma	3.5
2000	Abbott	Knoll (BASF Pharma)	7.0
2000	Glaxo Wellcome	SmithKline Beecham	72.4
2000	Pfizer	Warner-Lambert	87.3
1999	Pharmacia Upjohn	Monsanto	26.9
1998	Rhone-Poulenc Rorer	Hoechst AG	21.2
1998	Sanofi	Synthelabo	9.2
1998	Zeneca	Astra	34.6
1997	Hoffmann-La Roche	Boehringer Mannheim	11.0
1996	Sandoz	Ciba-Geigy	60.0**
1995	Glaxo	Burroughs Wellcome	20.0
1995	Hoechst-Roussel	Marion Merrell Dow	7.1
1995	Pharmacia	Upjohn	13.0**
1995	Rhone-Polenc Rorer	Fisons	2.7
1995	American Home	American Cyanamid	9.2
1994	Hoffmann-La Roche	Syntex	5.3
1994	Sanofi	Sterling	1.9
1990	Beecham	SmithKline Beckman	6.5**

*Source: Deutsche Ban, bloombergk *Pending **Value of merged entity*

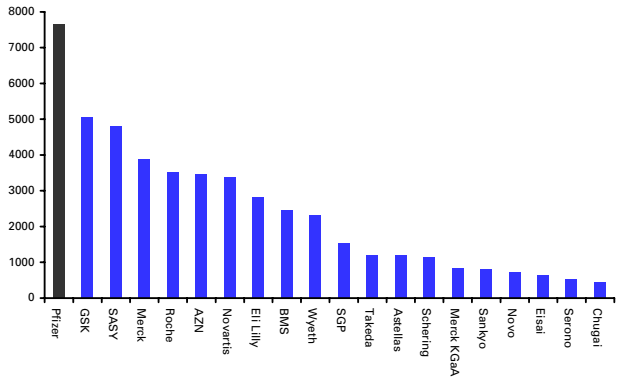
Looking at these deals, there can be little doubt that the factors discussed overleaf played an important role. However, these mega-combinations have also been driven by a desire to gain a greater share of the global market and to begin to dominate the market place. They have recognised that in an age when research productivity is faltering, patent expiries looming and the market shifting towards one that is more consumer driven, absolute market strength has its attractions. Not least among these are strong leverage with the key buyers of drug, the ability to afford greater marketing muscle behind key growth drivers and the ability to get more from all the assets in the portfolio. In effect, they have further raised the competitive bar. Indeed, one glance at the following charts depicting the enlarged Pfizer's standing vis-à-vis its competitors should help to emphasise just how formidable competing against this company is likely to be. All told, our opinion is that the costs of competing are rising and the experience of the past has demonstrated only too well that standing still is not an option.

Figure 29: Market capitalisation 2004 ($bn)



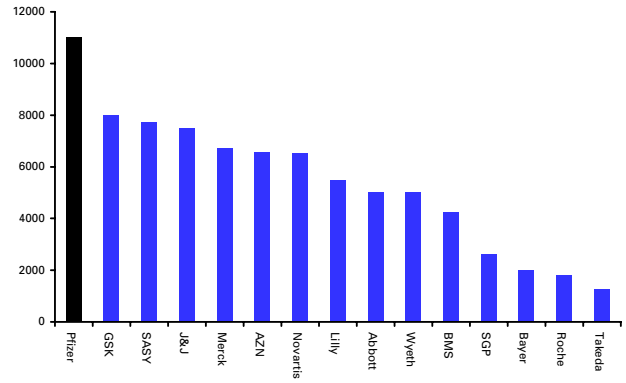
Source: Deutsche Bank

Figure 30: R&D expenditure, 2004 ($m)



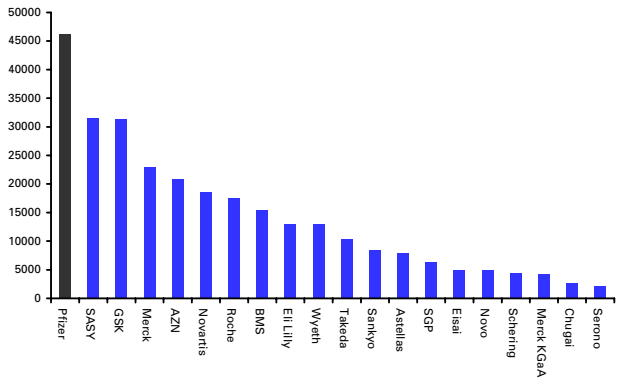
Source: Deutsche Bank

Figure 31: US salesforce size, 2004



Source: Deutsche Bank

Figure 32: Prescription drug sales, 2004 ($m)



Source: Deutsche Bank

Therapeutic strengths indicate greater concentration

Yet despite all of this merger activity, the industry in aggregate can still be described as fragmented. As mentioned earlier, market shares have concentrated and today's top ten companies account for around 55% of global market revenues compared to around 25% two decades earlier.

These simple statistics do, however, belie a far greater market concentration if different therapeutic markets are considered. For example, in the $90bn cardiovascular market, Merck, Pfizer and Sanofi-Aventis have almost a 50% market share between them. Similarly, in the $12bn asthma market, Glaxo alone has a market share of over 35%. Consequently, while the industry may still be fragmented from a total market perspective, by therapeutic area, concentration is often much greater. Companies have most definitely established strong franchises in different therapeutic markets.

Importantly, these franchises have real value over and above potential economies of scale. Strong association with a particular disease and the medical fraternity will most likely spawn greater confidence in new drugs introduced by the franchise company. Equally, the franchise company will most likely be seen as an attractive candidate for in-licensing or co-marketing opportunities, providing it with the opportunity to strengthen its hold further. However, if new products selling into the franchise market are not developed, franchises can also prove transient. As illustrated only too clearly by Glaxo's failure to build on the huge success of Zantac, loss of patent protection and years of marketing investment in building a franchise can disappear rapidly. For reference purposes, we summarise the therapeutic strengths of the leading industry players on the following page.

Figure 33: Therapeutic strengths and key products of the leading global pharmaceutical companies

	Anti-infective	Cardiovascular	CNS	Gastro-intestinal	Hormones	Metabolism	Musculoskeletal	Oncology	Respiratory	
AstraZeneca		✓✓ Crestor, Atacand	✓✓ Seroquel	✓✓✓ Nexium				✓✓ Arimidex	✓✓ Pulmicort	
Astellas				✓ Gaster						Tra
BMS	✓✓ Reyataz	✓✓ Pravachol				✓ Glucophage		✓✓ Taxol		
Eli Lilly			✓✓ Zyprexa, Strattera			✓✓✓ Insulin	✓✓ Evista	✓✓ Gemzar, Alimta		
GSK	✓✓✓ Combivir		✓✓✓ Paxil, Imitrex	✓ Zantac		✓✓ Avandia			✓✓✓ Advair	Va
Merck & Co	✓ Crixivan	✓✓✓ Zocor					✓✓ Fosamax		✓✓ Singulair	Ophth Va
Novartis		✓✓✓ Diovan	✓ Tegretol, Clozaril				✓✓ Voltaren	✓✓ Gleevec, Zometa		Ophth
Roche	✓✓ Pegasys					✓ Xenical		✓✓✓ Avastin, Rituxan		Tra
Pfizer	✓✓ Zithromax	✓✓✓ Lipitor	✓✓✓ Zoloft, Neurontin		✓✓ Genotropin		✓✓✓ Celebrex	✓ Camptosar	✓✓ Zyrtec	Erectile Ophth
Schering-Plough	✓✓ PEG-Intron	✓ Zetia, Vytorin							✓✓ Clarinex	
Sanofi-Aventis	✓ Ketek	✓✓ Plavix, Lovenox	✓✓ Ambien			✓✓ Lantus	✓✓ Actonel	✓✓ Taxotere, Eloxatin	✓✓ Allegra	Va
Takeda		✓ Blopress		✓✓ Prevacid		✓✓ Actos		✓ Lupron		
Wyeth	✓ Zosyn		✓✓ Effexor	✓✓ Protonix	✓✓✓ Premarin		✓✓ Enbrel			Va

✓✓✓ >15% market share ✓✓ 5-15% market share ✓ Good presence

Source: Deutsche Bank

Who's got and who's not?

Looking through company pipelines at the present time, it is evident that the industry is suffering from a real dearth of exciting new drugs. Indeed, the pipelines of the major pharmaceutical companies are today looking thinner than they have done for several years. At the same time, over the next five years, many of the major companies look set to lose patent protection on several large and important drugs. All told, this does not bode well for the growth prospects of many of today's industry leaders.

So who's got and who's not? The following tables summarise in brief, the pipeline potential and expiry risks of each of the global majors. What is most striking is that of the US and European majors, Merck, Schering-Plough and AstraZeneca look as though they have little of real interest in the cupboard in terms of near term NCE launches. Elsewhere, the apparently strong profile of Roche is primarily due to Avastin which was launched in 2004, while several of the other new drugs in development at the company have a signficiant risk of being dropped, in our view. Overall, Lilly and Bristol-Myers are well positioned with several near term launches that offer significant commercial opportunity, while amongst the Europeans, Novartis has the most interesting late stage pipeline. In addition, including the Zetia/Zocor combination product Vytorin into the forecasts for Merck and Schering-Plough would suggest significantly greater replacement potential.

Figure 34: Who's got and who's not?

Company	2004 value of sales exposed to US expiry to 2008E	Major expiry year	% 2004 total sales	2008E value of launches in 2004-2008E	Key launch year	% of 2004 sales
European						
AstraZeneca	$1.4bn	2007	6%	$0.6bn	2008	3%
GSK	$6.5bn	2007	21%	$3.8bn	2007	12%
Novartis	$2.2bn	2007	12%	$2.7bn	2007	15%
Roche	$0.7bn	2005	5%	$6.1bn	2004	37%
Sanofi-Aventis	$4.0bn [1]	2006	13%	$3.0bn	2006	10%
United States						
Bristol-Myers	$3.1bn	2006	20%	$2.7bn	2005	17%
Eli Lilly	$0.3bn	2006	2%	$3.9bn	2004	30%
Merck	$6.0bn	2006	26%	$2.2bn [2]	2007	10%
Pfizer	$10.4bn	2006	23%	$5.4bn	2005	12%
Schering-Plough	$0.5bn	2007	7%	$0.8bn [2]	2005	12%
Wyeth	$2.8bn	2008	22%	$2.3bn	2007	16%

Source: Deutsche Bank estimates [and company date?](1) Assumes expiry of Allegra in 2006 (2) Does not include non-consolidated sales of Vytorin (launched in 2004, 2008E sales $2.4bn)

European companies – Summary pipelines & expiries 2004-2007E

Figure 35: AstraZeneca

Patent expiries	2004 US Sales	% Pharma	Expiry date
Plendil	$166m	1%	2004
Zoladex	$152m	1%	2005
Pulmicort	$576m	3%	2007
Toprol	$977m	5%	2007

New product	Peak sales	Indication	Launch date
Symbicort (US)	$1,000m	Asthma	2007

Source: Company data, Deutsche Bank estimates

Figure 36: GSK

Patent expiries	2004 US Sales	% Pharma	Expiry date
Wellbutrin	£410m	2%	2004
Flonase	£450m	3%	2005**
Zofran	£565m	3%	2007
Coreg	£425m	2%	2007
Imitrex	£492m	3%	2007*

New product	Peak sales	Indication	Launch date
Vesicare	$400m	Incontinence	2005
Boniva	$500m	Osteoporosis	2005
nelarabine	$200m	Leukaemia	2005
Rotarix	$500m	Rotavirus (vaccine)	2006
640385	$200m	HIV	2007
Avamys ('698)	$500m	Allergy	2007
597599	$300m	Emesis	2007
Cervarix	>$1,000m	HPV (vaccine)	2007

**Assumes litigation successful* ***Pending issue of FDA guidance*

Source: Company data, Deutsche Bank estimates

Figure 37: Novartis

Patent expiries	2004 US Sales	% Pharma	Expiry date
Lotensin	$77m	<1%	2004
Trileptal	$391m	2%	2006
Lamisil	$528m	3%	2007
Tegretol XR	$103m	1%	2007
Lotrel	$920m	5%	2007*

New product	Peak sales	Indication	Launch date
Enablex	$350m	Incontinence	2005
Certican	$300m	Transplant	2005/6
Exjade (ICL670)	$500m	Iron overload	2005/6
LDT600	$150m	Hepatitis B	2006
LAF237	$500m	Diabetes	2007
SPP100	$350m	Hypertension	2007
Lucentis	$500m	AMD	2007

**Assumes litigation unsuccessful*

Source: Company data, Deutsche Bank estimates

Figure 38: Roche

Patent expiries	2004 US Sales	% Pharma	Expiry date
Rocephin	CHF 796m	4%	2005

New product	Peak sales	Indication	Launch date
Avastin	>$2,000m	Colorectal cancer	2004
Tarceva	$800m	Lung cancer	2004
Boniva	$500m	Osteoporosis	2005
CERA	>$1,000m	Anaemia	2007
Lucentis	$500m	AMD	2007

Source: Company data, Deutsche Bank estimates

Figure 39: Sanofi-Aventis

Patent expiries	2004 US Sales	% Developed sales	Expiry date
Amaryl	Euro 216m	1%	2005
Ambien	Euro 1,164m	4%	2006
Allegra	Euro 1,197m	4%	2006*

New product	Peak sales	Indication	Launch date
Ketek (US)	$1,500m	Bacterial infection	2004
Ambien CR	$500m	Insomnia	2005
Menactra	$600m	Meningitis (vaccine)	2005
Apidra	$250m	Diabetes	2006
Alvesco	$1,000m	Asthma	2006
Acomplia	$800m	Obesity	2006
Exubera	$1,000m	Diabetes	2006
dronedarone	$300m	Arrhythmia	2006

**Assumes litigation unsuccessful*

Source: Company data, Deutsche Bank estimates

Figure 40: Schering

Patent expiries	2004 US Sales	% Pharma	Expiry date
Yasmin	Euro 211m	6%	2007*

New product	Peak sales	Indication	Launch date
Angeliq (US)	$300m	HRT	2005/6
Yaz (Yasmin 20)	$200m	Contraception	2005/6
asoprisnil	$200m	Uterine fibroids	2006

**If litigation successful*

Source: Company data, Deutsche Bank estimates

US companies – Summary pipelines & expiries 2004-2007E

Figure 41: Bristol-Myers Squibb

Patent expiries	2004 US Sales	% Pharma	Expiry date
Glucophage XR	$67m	<1%	2004
Glucovance	$165m	1%	2004
Paraplatin	$537m	3%	2004
Cefzil	$161m	1%	2005
Pravachol	$1,426m	9%	2006
Videx	$105m	1%	2007

New product	Peak sales	Indication	Launch date
Erbitux	$700m	Colorectal cancer	2004
Baraclude	$500m	Hepatitis B	2005
abatacept	$750m	Rheumatoid arthritis	2005
muraglitazar	>$1,000m	Diabetes	2007
ixabepilone	$500m	Cancer	2007

Source: Company data, Deutsche Bank estimates

Figure 42: Eli Lilly

Patent expiries	2004 US Sales	% Pharma	Expiry date
Actos	$340m	2%	2006*

New product	Peak sales	Indication	Launch date
Cymbalta	$1,500m	Depression	2004
Alimta	$750m	Lung cancer	2004
Yentreve	$750m	SUI	2004 (EU)
Byetta	$750m	Diabetes	2005
ruboxistaurin	$1,000m	Diabetic neuropathy	2006
prasugrel	$1,000m	Thrombosis	2007

**US rights returned*

Source: Company data, Deutsche Bank estimates

Figure 43: Merck

Patent expiries	2004 US Sales	% Pharma	Expiry date
Proscar	$368m	2%	2006
Zocor	3613	16%	2006

New product	Peak sales	Indication	Launch date
Vytorin	>$2,000m	Cholesterol	2004
Gardasil	$1,500m	HPV (vaccine)	2006
Zostavax	$1,000m	Shingles (vaccine)	2006
RotaTeq	$500m	Rotavirus (vaccine)	2006
muraglitazar	>$1,000m	Diabetes	2007
MK-431	$750m	Diabetes	2007

Source: Company data, Deutsche Bank estimates

Figure 44: Pfizer

Patent expiries	2004 US Sales	% Pharma	Expiry date
Accupril	$387m	1%	2004
Diflucan	$417m	1%	2004
Neurontin	$2,198m	5%	2004
Zithromax	$1,393m	3%	2005
Zoloft	$2,657m	6%	2006
Camptosar	$550m	1%	2007
Norvasc	$1,991m	4%	2007

New product	Peak sales	Indication	Launch date
Spiriva	$1,500m	COPD	2004
Lyrica	>$1,000m	Neuropathic pain	2005
Macugen	$500m	AMD	2005
Oporia	$750m	Osteoporosis	2005
indiplon	$750m	Insomnia	2006
Exubera	>$1,000m	Diabetes	2006
Sutent	$750m	Renal cancer	2006
varenicline	$500m	Smoking cessation	2006
maraviroc	$500m	HIV	2007

Source: Company data, Deutsche Bank estimates

Figure 45: Schering Plough

Patent expiries	2004 US Sales	% Pharma	Expiry date
Rebetol	$45m	1%	2004

New product	Peak sales	Indication	Launch date
Vytorin	>$2,000m	Cholesterol	2004
Noxafil	$500m	Fungal infections	2005
garenoxacin*	$300m	Bacterial infections	2006
SCH-D	$500m	HIV	2007

**US rights to be sublicensed*

Source: Company data, Deutsche Bank estimates

Figure 46: Wyeth

Patent expiries	2004 US Sales	% Pharma	Expiry date
Zosyn	$395m	3%	2007

New product	Peak sales	Indication	Launch date
Tygacil	$500m	Bacterial infections	2005
Librel	$300m	Contraceptive	2006
bazedoxifene	$500m	Osteoporosis	2007
tanaproget	$300m	Contraceptive	2007
DVS-233	$1,000m	Depression	2007
bifeprunox	$500m	Schizophrenia	2007
temsirolimus	$300m	Cancer	2007

Source: Company data, Deutsche Bank estimates

The leading drugs

Top ten drugs account for 10% of industry revenues

Recent years have seen a dramatic increase in the number of blockbuster drugs, that is, drugs achieving sales over $1bn. In addition, the proportion of global industry revenues represented by the ten leading drugs has increased from around 5% in 1985 to around 10% today. Indeed, the world's largest drug in 2004, Pfizer's Lipitor, looks set to account for over 2% of industry revenues in its own right. This is more than the global market share of all but the top 13 drug companies alone!

Given the economies of scale associated with a single product realising in excess of $1bn in sales, the increase in the number of blockbuster products has done much for industry profitability. However, despite consolidation, the overall increase in the absolute size of key drugs suggests that pharmaceutical portfolios remain as exposed to patent expiries on large products today as was the case a decade or so ago.

Figure 47: The world's leading drugs by revenues in 2004 ($m)

Rank	Product	Indication/Category	Company	Sales
1	Lipitor	Hypolipidaemic	Pfizer	10862
2	Zocor	Hypolipidaemic	Merck & Co.	5197
3	Advair	Asthma	GlaxoSmithKline	4508
4	Norvasc	Hypertension	Pfizer	4463
5	Zyprexa	Anti-psychotic	Eli Lilly	4420
6	Nexium	Proton pump inhibitor	AstraZeneca	3883
7	Procrit/Eprex	Erythropoietin	Johnson & Johnson	3589
8	Zoloft	Anti-depressant	Pfizer	3361
9	Effexor	Anti-depressant	Wyeth	3347
10	Plavix	Anti-thrombotic	Sanofi-Aventis/BMS	3327
11	Celebrex	NSAID	Pfizer	3302
12	Fosamax	Osteoporosis	Merck & Co.	3160
13	Diovan	Hypertension	Novartis	3093
14	Risperdal	Anti-psychotic	Johnson & Johnson	3050
15	Cozaar/Hyzaar	Hypertension	Merck & Co.	2824
16	Neurontin	Anti-convulsant	Pfizer	2723
17	MabThera	Non-Hodgkin's lymphoma	Roche/Genentech	2719
18	Pravachol	Hypolipidaemic	Bristol-Myers Squibb	2635
19	Singulair	Asthma/Allergy	Merck & Co.	2622
20	Epogen	Erythropoietin	Amgen	2601
21	Prevacid	Proton pump inhibitor	TAP	2592
22	Aranesp	Erythropoietin	Amgen	2473
23	Insulin	Insulin	Novo Nordisk	2402
24	Lovenox	Anti-thrombotic	Sanofi-Aventis	2372
25	Remicade	Rheumatoid arthritis	Johnson & Johnson	2145

Source: Company information

Concentration owes much to marketing

The reason for this dramatic concentration and the significant increase in blockbuster products goes beyond the discovery of new drugs selling to potentially large patient populations. The shortening of time between the introduction of first-in-class and me-too products has meant that the industry majors have recognised the importance of rapidly establishing new products in the marketplace and building a dominant share ahead of the introduction of competitors. Consequently, huge resources are now put behind drug launches as companies seek to maximise physician and patient awareness. For example, AstraZeneca spent over $300m on the launch of Crestor, its cholesterol-lowering drug introduced in 2003. In addition, key pharmaceutical products are now launched almost simultaneously worldwide, instead of on a gradual country-by-country basis. This dynamic approach to product launches serves to maximise the net present value of a new drug over its lifetime, with peak sales levels attained earlier in a drug's lifecycle. Management of the lifecycle of new drugs through the use of different formulations (for example, once-a-day, extended release, injectables), together with attempts to attain approval for a broader range of indications, have also played an important role in bolstering total sales.

Hyperlipidaemics lead the blockbuster charts

The first product to achieve annual sales of over $1bn was SmithKline's anti-ulcer drug, Tagamet, in 1986. By 1990, seven drugs had attained blockbuster status. Today, over 80 drugs achieve sales of over $1bn, with the leading 20 achieving sales at least twice this level.

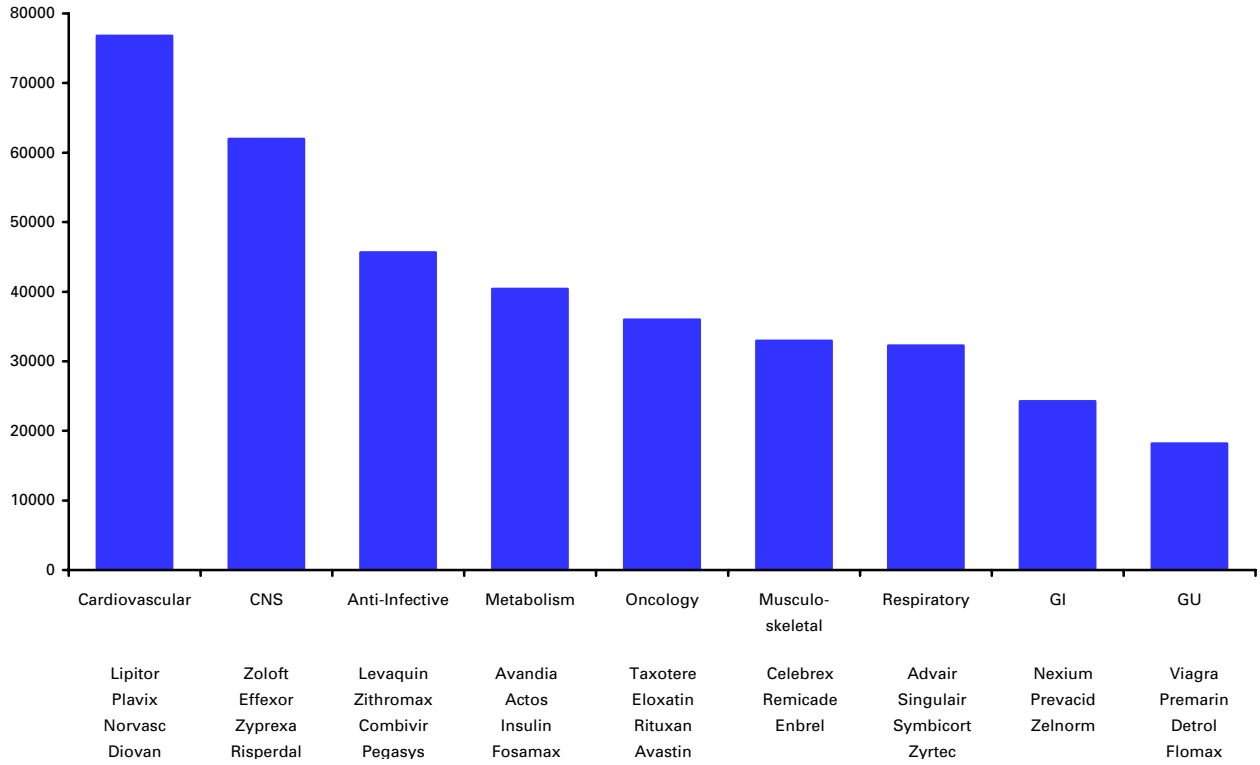
Indeed, until 2001, a drug for ulcers/acid reflux had for 15 years consistently topped the list of industry best sellers (Tagamet, followed by GSK's Zantac and then AstraZeneca's Prilosec). However, the rapid growth of the cholesterol lowering drugs, such as Pfizer's Lipitor and Merck's Zocor, combined with Prilosec's recent patent expiry, have seen a new class emerge as the industry leader. With several years of patent life still to run and considerable further scope for market expansion, these drugs look set to continue to dominate the tables, over the next few years. Quite what will follow them is, however, unclear at this stage.

The dominant therapeutic categories

By examining industry revenues by therapeutic class, it is evident that the most significant categories are those for cardiovascular products (including the cholesterol reducers), diseases of the central nervous system, antibiotics, gastro-intestinal products and respiratory disorders. Each of these categories incorporate drugs that typically target a large and growing patient population.

In particular, cardiovascular markets stand out as representing a major class. Of the world's 25 best-selling drugs, seven are cardiovascular, of which three are cholesterol-lowering agents. Worth over $22bn in its own right, this cardiovascular sub-sector continues to record growth of over 10% per annum. Similarly, six of the world's top 25 drugs are CNS agents, of which the $11bn anti-psychotics (schizophrenia) market is registering double-digit growth per annum. However, the patent expiration of a best-selling drug can have a significant effect on value growth of the relevant therapeutic class, as has been evident following the arrival of generic versions of several leading antibiotics or the patent expiration of the best-selling anti-ulcerant, Prilosec.

Figure 48: The major therapeutic categories and leading drugs



Source: Wood Mackenzie

Super drugs of tomorrow

So what will be the super drugs of tomorrow? Looking at current pipelines, the list of candidates appears rather limited. Leaving aside the multitude of second generation and me-too products in development, some of the more interesting and innovative products include:

- **New cancer treatments.** This is perhaps the most exciting area for drug development as new, targeted drugs have been shown to offer significant survival benefits without the severe side effects associated with traditional cancer therapies. Of particular interest are drugs that inhibit angiogenesis or the growth of new blood vessels. By inhibiting a protein known as vascular endothelial growth factor (VEGF), anti-angiogenesis drugs aim to starve tumours of essential nutrients by preventing the growth of new blood vessels. Launched in 2004, Roche/Genentech's anti-VEGF antibody Avastin has shown impressive results across a number of solid tumour types and is rapidly on the way to blockbuster status. Many other novel drugs are in late stage development, which target VEGF or other proteins implicated in tumour growth such as EGFR, HER2, c-Kit, raf kinase and others. Key drugs to watch include Pfizer's Sutent, Bayer's sorafenib, GSK's lapatinib and Pfizer's AG-13736.
- **Oral clot-busters.** Several drugs are in development for the prevention of blood clots in patients undergoing orthopaedic surgery, or those who are at high risk of a heart attack due to an irregular heartbeat. While there are existing treatments in both areas, they are either injectible or difficult to control, with considerable risk of side effects. Consequently, much attention is focused on developing a safe, convenient and effective oral treatment. The most advanced compounds in this area include those that inhibit an enzyme known as Factor Xa, such as Bayer's BAY59-7939 and Bristol-Myer's razaxaban, and others, such as Boehringer Ingelheim's BIBR1048, AstraZeneca's AZD0837 and GSK's Odiparcil, which aim to directly or indirectly inhibit the protein thrombin.

- **Oral multiple sclerosis drugs.** Multiple sclerosis (MS) is a progressive, autoimmune disease which is currently treated with a class of drugs known as the interferons. However, all of the currently marketed drugs are injected and offer only modest efficacy. Thus considerable effort has been devoted to developing a product that can either improve upon the efficacy of the existing treatments and/or offer greater convenience by being administered as a pill. Competing in a neck-and-neck race to become the first oral MS drug are Serono's Mylinax (cladribine) and Novartis' FTY720. Both should be in Phase III by the end of 2005 with regulatory filings likely in 2008.
- **HPV vaccines.** Cervical cancer is responsible for over 270,000 deaths per year, including 36,000 deaths in North America and Europe. All cervical cancers are caused by a sexually-transmitted virus called human pappilomavirus (HPV), with two strains, HPV16 and HPV18, responsible for over 70% of all cases. Merck and GlaxoSmithKline are both developing vaccines which target these two cancer-causing strains. Merck's vaccine Gardasil (slated for filing in 2005) also protects against two additional strains, HPV6 and HPV11, which are associated with most cases of genital warts. While GlaxoSmithKline's product Cervarix only directly targets HPV16 and HPV18, it has demonstrated cross-protection against a number of other HPV strains that cause an additional 10% of cervical cancer cases.

Large areas of unmet medical need

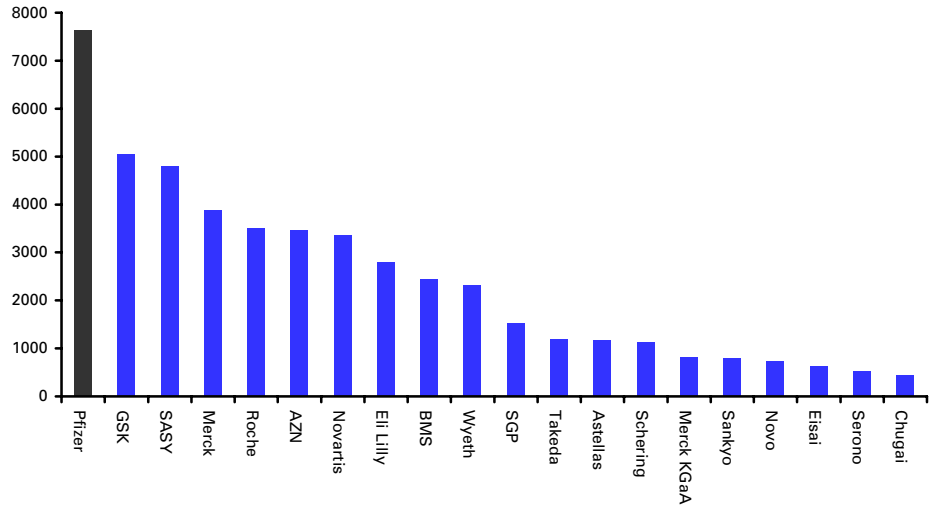
Outside these new drugs, several large diseases still do not have effective treatments. Amongst these, and excluding the largest market of them all, cancer, the diseases with the greatest commercial potential include the following:

- **Stroke.** Stroke remains a major killer for which there is no effective treatment. To date, the disorder has represented a graveyard of pharmaceutical ambitions. AstraZeneca's neuroprotectant Cerovive has shown promising efficacy in the first of three Phase III trials. If the safety and efficacy of the drug are confirmed in subsequent studies, Cerovive could easily achieve blockbuster status.
- **Alzheimers.** Over 10% of the over 65 population suffers from Alzheimer's disease, a degenerative brain disorder in which memory and function are gradually impaired. The disease poses a huge cost to society. Several new treatments have been developed, not least Eisai/Pfizer's Aricept, Novartis' Exelon and J&J/Shire's Razadyne (formerly Reminyl). Yet these drugs have only been shown to slow the rate of degeneration by around 12-24 months. More effective treatments would offer huge sales potential.
- **Obesity.** As we become ever more sedentary, so we are becoming more obese. Roughly 25% of the US population is now suggested to be obese, with Europe not far behind. Drugs that aid weight loss hold huge potential, both for their health and lifestyle benefits. Xenical, a treatment from Roche, looked to offer hope, but side effects are unpleasant and efficacy limited. However, Phase III studies for Sanofi-Aventis's Acomplia have shown a more promising efficacy and side effect profile, including significant benefits on related metabolic parameters. The market potential for an effective drug in this class is huge, although patient compliance has been shown to be a challenge.
- **Emphysema (COPD).** The ravages of smoking are becoming more evident in society and not just through cancer. One of the risks of long-term smokers is damage to the airways and pockets in the lungs, resulting in chronic bronchitis or emphysema. There is a significant market for drugs that can ease the symptoms of this disorder. Key here are drugs such as Pfizer/BI's Spiriva and a class of development projects called the PDE4 inhibitors.
- **Neuropathic pain and diabetes**. Diabetes is an awful disease the effects of which are wide ranging. Among other things, these include destruction of the blood vessels feeding, for example, the limbs and eyes. Drugs for treatment of diabetes and its side effects, such as neuropathic pain (tingling and pain associated with nerve wasting), offer huge potential.

The R&D process

Research and development (R&D) is the lifeblood of the industry. It is only through innovation and the launch of new and effective forms of medicine that the pharmaceutical industry can continue to grow. Consequently, the major pharmaceutical companies have, without exception, substantially increased their total investment in research and development over the past decade. We estimate that the top ten industry participants spent over $30bn on research in 2004. This corresponds to around four times the level of spending in 1990.

Figure 49: Research & development spending by company in 2004 ($m)



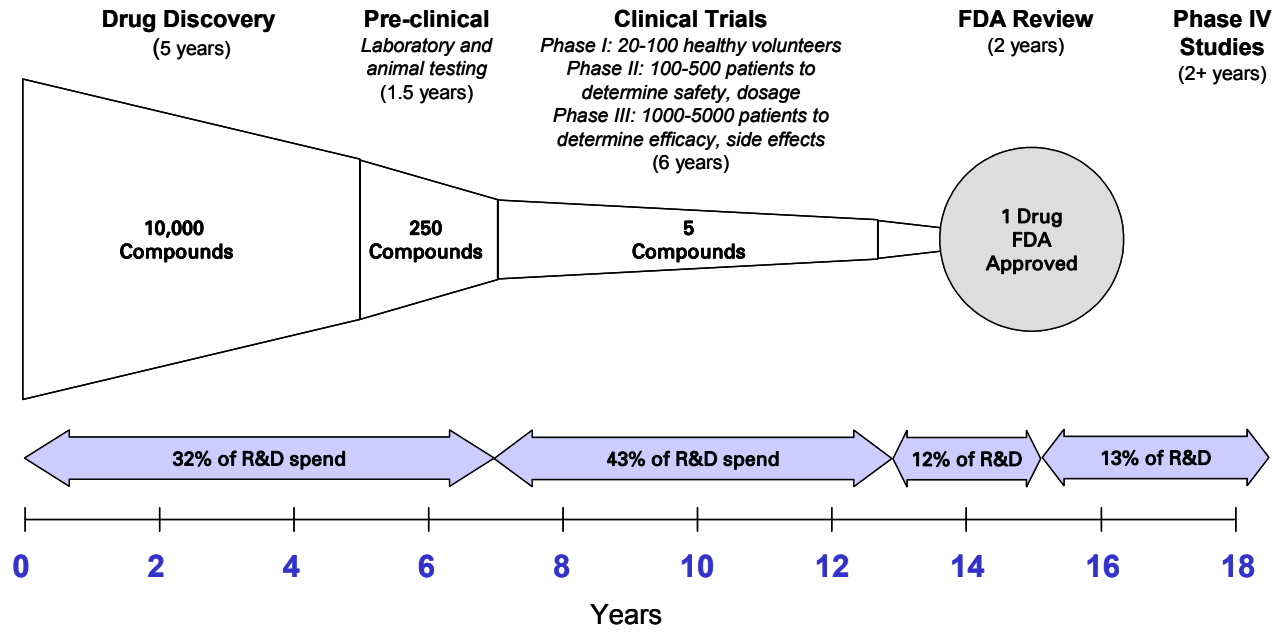
Source: Company data, Deutsche Bank estimates

The drug discovery process is clearly time-consuming, complex and highly risky. From start to finish, industry estimates suggest that of the 5,000-10,000 molecules screened in the discovery process, only one will make it to market as an approved drug. As molecules become more complex and safety regulations ever more stringent, the costs of developing a pharmaceutical have increased dramatically. Today, it is estimated that, if the$300-350m cost of failures is included, the average successful new drug costs nearly $900m before tax to bring to market. This compares to an estimated $230m at the end of the 1980s. Equally, the time taken from discovery to market has increased dramatically over the past 20 years, rising from around 11 years in 1980 to nearer 15 years today.

As illustrated by the above industry estimates of the cost now required to develop and successfully launch a new drug, industry productivity has clearly not kept pace with research costs. While almost every major drug company targets bringing two to three new products to the market each year, few appear anywhere near achieving their goal. To date, the costs of improving industry productivity and industrialising the research process appear to be little more than just that - further costs. In our opinion, the paucity of interesting products in the late-stage pipelines of the major companies also suggests a lack of innovation. All things considered, the industry remains hugely dependent on basic scientific discovery and the industry can only develop solutions as the complexities and mechanisms of human biochemistry are unravelled.

As illustrated in Figure 50, the research and development programme for drug development comprises several distinct phases that can broadly be divided into discovery, pre-clinical, clinical and post-marketing. On average, we estimate that company spending on R&D is allocated broadly one-third discovery/pre-clinical and two-thirds clinical, with roughly 35% of discovery/pre-clinical spending allocated to financing research within external organisations. The key features of each of these, together with a definition of certain terms, are described below.

Figure 50: The process of research and development – stages and timing



Source: PhRMA Industry Profile 2005

Discovery

In the discovery phase, several hundred thousand chemical entities will typically be screened for a pharmacological effect. The length of time this process can take is anything from two to ten years, although new technologies are helping to significantly reduce the discovery process, not least high-throughput screening, combinatorial chemistry and an increasing knowledge of genomics (as detailed later on in this report).

The process of drug discovery begins with knowledge about the disease. This knowledge is generally developed through basic research - conducted not only in the laboratories of the pharmaceutical companies, but also in government, university and biotechnology company laboratories and mainly funded by the major pharmaceutical houses. Basic research reveals disease mechanisms or processes that become the targets of pharmaceutical intervention. It can be likened to the exploratory phase of scientific and drug research, where understanding of disease or functional pathways is sought and potential drug targets identified. Clearly, basic research in any scientific area is an ongoing event. However, exploratory work on determining specific drug targets generally averages 12 months.

Once the potential drug target is identified, the drug companies will attempt to develop a molecule that interacts with that target and which might form the basis of a drug. Techniques such as combinatorial chemistry come into play, as companies use rational drug design in an attempt to design a molecule that may interact with the identified target. Companies may also screen their chemical libraries as they seek potential drug candidates. On average, companies may spend a year developing lead candidates. These early drug candidates will then be assessed using techniques such as high throughput screening (HTS) to determine

the quality of the drug-target interaction. Molecular imaging is also used to try to assess drug interaction and the first in vitro tests will be undertaken on animal tissue to see whether the drug has any physical effect on animal cells, that is, does the concentration of various chemicals, such as calcium, which are known to play a role in cell activity, alter? Overall, tens of thousands of molecules may be screened to see if they have a potential pharmacological effect, but over a period of two to three years, only a handful may move forward for pre-clinical evaluation.

Combinatorial chemistry: Combinatorial chemistry is the synthesis of a substantial number of distinct compounds using similar reaction conditions. The process incorporates systematic molecular design, either by linking separate building blocks or by adding substituents to a core structure. As the process is fully automated or computerised, the 1,000-2,000 compounds required to identify three to four possible candidates can be screened in a matter of months. Many of the large international drug companies, as well as the smaller molecular design companies, have established extensive molecular libraries detailing the synthesis techniques, physicochemical properties and any experimental data, such as toxicology or pharmacokinetic studies. Overall, it is estimated that combinatorial chemistry has resulted in a18-24 month reduction in the time taken to identify drug candidates.

High-throughput screening: HTS utilises computer-controlled robotic systems for testing compounds systematically through a wide range of assays. The compounds identified from combinatorial chemistry are bar coded, weighed and dissolved in a range of standard solutions and then screened using a wide range of assays. These will include both the traditional assays and a wide range of new bacterial or human cell assays, which provide a closer proxy for the conditions in the human body. Automated HTS has replaced what was previously a time consuming and costly manual process and has contributed extensively to chemical information libraries.

The pre-clinical phase

Ultimately, using these techniques and others, a handful of drug candidates will be taken forward for pre-clinical testing in animals (in vivo or in the body) and further laboratory analysis (in vitro or outside the body) and the key pharmacological characteristics of a compound determined. These characteristics are summarised by the acronym ADMET, which stands for absorption, distribution, metabolism, excretion and toxicology. These determine the suitability of a new chemical to become a drug. If a compound appears to have important biological activity and may be useful as a drug, tests evaluating the ADMET criteria are conducted on the major organ systems (such as CNS, cardiovascular and respiratory systems). Other organ systems are evaluated when potential problems appear. These pharmacology studies are conducted in animals to ensure that a drug is safe to be tested in humans.

An important goal of these pre-clinical animal studies is to characterise any relationship between increased drug doses and toxic effects. Drug development will be halted if tests suggest that a significant risk may be posed in humans – especially organ damage, genetic defects, birth defects and cancer. On average, drug candidates can spend around four years in the pre-clinical stage.

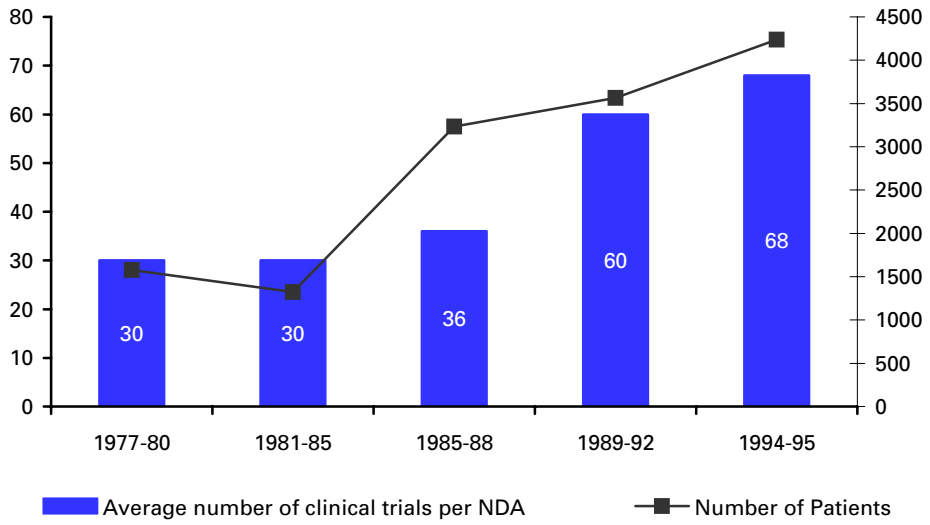
Clinical studies in humans

A drug sponsor may begin clinical studies in humans once the FDA is satisfied that the pre-clinical animal data does not show an unacceptable safety risk to humans. The pharmaceutical company will file an investigational new drug (IND) application with the regulatory authorities. Once approved, human trials can begin, although at all stages, sponsors and investigators must follow regulations designed to ensure safety. Indeed, for US applications, an Institutional Review Board must review and approve a research plan before the trial begins and thereafter continuously monitor the clinical process.

There are four main phases of clinical trials in drug development and a new drug application, or NDA, will typically involve almost 70 clinical trials involving more than 4,000 patients. The definitions are functional and drug development candidates need not necessarily pass through one phase before the next is undertaken, that is, clinical trials may overlap. Equally, it is important to appreciate that a drug may be in different phases of the trial process for different indications. In other words, a drug may be approved for use in, say, hypertension, but still going through the clinical process for, say, congestive heart failure.

- **Phase I trials** represent initial safety trials on a new medicine. They are usually conducted in a small number of healthy male volunteers and are undertaken to establish the dose range tolerated by volunteers, as well as to gain further knowledge on the pharmacokinetics of the drug in humans. In the case of drugs for the treatment of life-threatening diseases, such as cancer, Phase I trials are usually conducted in ill patients, rather than healthy volunteers. Trials typically involve 20-100 patients and account for less than 10% of total R&D spending. Typically, around 80-90% of Phase I drug candidates fall by the wayside.

Figure 51: Trials and patient numbers per new drug application



Source: Boston Consulting Group

- **Phase II trials** are conducted to evaluate efficacy and safety in selected populations of patients with the disease or condition to be treated or prevented. Objectives typically focus on dose response and dosing frequency, together with safety, efficacy and side-effect characteristics. Trials typically involve 100-500 patients and fewer than 40% of Phase II drug candidates will progress to Phase III. In total, we estimate Phase II trials account for around 10-15% of R&D budgets. Note that a Phase IIb trial is typically a larger and more rigorous demonstration of a medicine's efficacy, while a Phase IIa study can be thought of as a proof of concept study (i.e. the trial is seeking to demonstrate that the concept works).
- **Phase III trials** are typically conducted once the efficacy of a medicine has been demonstrated and the optimal dose range determined. Again, they are conducted in patients for whom the medicine is intended and are designed to demonstrate safety and efficacy in larger patient populations. Several trials may be conducted as the sponsor of the trials seeks to demonstrate the benefit of the drug against placebo, in combination with other treatments or relative to an existing treatment. The number of patients involved will depend on the disease for which the drug is intended. A cancer drug may only be investigated in a few hundred patients, while a drug for hypertension would be

studied in several thousand. Key to determining the number of patients is the need to identify potentially rare side effects, as well as to perform statistical analysis on the results. No drug will gain approval unless it has shown statistically significant superiority to placebo in clinical trials, with the exception of cancer drugs, where the focus is on an increase in survival times. Phase III trials are often described as pivotal trials and will typically form the major part of the submission to the regulatory authorities. Phase III trials are estimated to account for around 30-35% of a company's R&D spending.

- **Phase IV or post-marketing surveillance.** Assuming the successful completion of at least two pivotal trials, the drug sponsor submits a new drug application (NDA) to the relevant regulatory authority, such as the FDA in the US, the EMEA in Europe or the MHLW in Japan, for approval to manufacture, distribute and market the drug. However, even if the drug is approved, the clinical process does not come to an end. Sponsors are required to undertake post-marketing surveillance to monitor a drug's safety, a process that continues for the life of the drug. The objective of such surveillance is simple. Adverse reactions that occur in fewer than one in 3,000-5,000 patients are unlikely to have been detected through the clinical process and may be unknown at the time the drug is launched. Thus, rare adverse events are more likely to be detected once the drug has exposure to a substantial patient population. Should serious adverse events occur anywhere in the world, the pharmaceutical companies must inform the regulatory agencies within 15 days. Depending upon the frequency and severity of the adverse event, changes to a drug's labelling, as was the case with Glaxo's Lotronex, or indeed its complete withdrawal, as happened with Bayer's Baycol, may be deemed necessary.

… But the clinical trial process continues

It is important to appreciate that almost all companies will continue to undertake clinical trials on launched drugs and to use the data gathered to strengthen the drug label (see the section on regulatory). This may be as they seek to develop further long-term data on the efficacy of the treatment or seek approval for additional indications, i.e., anti-depressant treatments are used not only for depression, but also for a number of other anxiety-related CNS indications (social phobia, obsessive compulsive disorder, etc). Equally, companies may undertake trials to demonstrate the greater efficacy or side-effect profile of the drug relative to a class competitor and so strengthen the drug's marketing message and appeal to physicians.

R&D productivity

One of the key issues for the industry today is R&D productivity. At a time when the industry is facing increased pressure on top-line growth, in light of patent expiries and the determination of payers globally to control the growth of expenditure on medicines, innovation is more important than ever for growth. After a wave of new drug launches through the mid-to-late 1990s, industry pipelines today very evidently show a dearth of innovative new products. And where companies do have a late-stage offering, many of these are 'me too' in nature. As such, they are unlikely to open new markets.

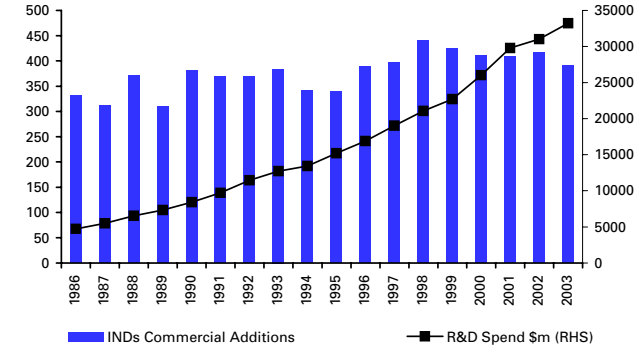
What is somewhat alarming is that while the amounts spent on R&D continue to rise, the industry's late-stage pipeline is showing precious few signs of expanding. As illustrated by Figures 52 and 53, although applications for investigational new drugs from commercial organisations are on the increase, the rate of increase is modest. Equally, failure rates have, if anything, been on the rise. As a result, while the number of molecules reported to be in Phases I and II has grown, the number of molecules in Phase III has not.

Whether this reversal in industry fortunes is permanent or transient remains to be seen. Certainly, a significant element of the decline in product successes can be attributed to several factors. Among other things, these likely include a more safety-conscious FDA, crowded therapeutic classes requiring products to be better differentiated, a greater risk of drug-drug interactions and the greater complexity of today's molecules. The industry's early

1990s shift towards more innovative (but unproven) mechanisms, as it feared the impact of a change in US market structure on the price of 'me-too' products, has also no doubt played its part.

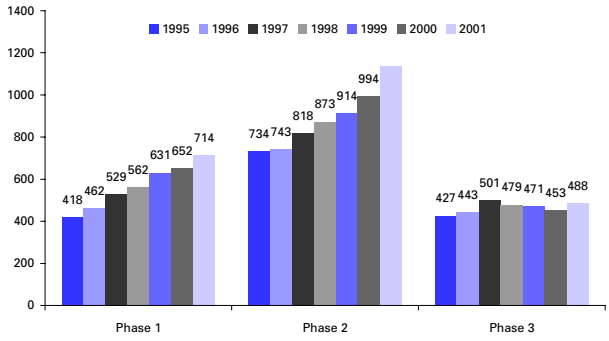
Yet, quite aside from any potential future benefit from the genomics revolution, the industry is undertaking research into a growing number of new receptor classes, many of which could result in significant new developments. In almost all areas of disease, new mechanisms are being actively sought. However, with today's pharmacopoeia already encompassing many very successful treatments, be they palliative or curative, the bar for success is far higher than ever before. Thus, with few clear signs of an imminent breakthrough in any significant new receptor class, the clear message for the time being must be that, despite all the industry's best efforts, the risks associated with successful pharmaceutical development continue to increase, while improvements in productivity do not. Serendipity has yet to show her hand.

Figure 52: IND filings fail to keep pace with R&D



Source: FDA; PhRMA

Figure 53: The late stage pipeline is static



Source: Pharmacoprojects

How do analysts assess R&D pipelines?

Given that a significant proportion of a pharmaceutical company's market capitalisation is tied up in the value of its R&D pipeline, it is not surprising that a major part of pharmaceutical analysis centres on assessing the potential of drugs in development. This is not an exact science and is probably the area of pharmaceutical analysis most prone to error.

Until recently, pipeline analysis could be summed up as 'spot the blockbuster' and focused on identifying high potential drugs in development. Most excitingly, these are drugs with a totally novel mechanism of action, targeted at a disease with large patient numbers, where there is a high level of unmet medical need. However, many blockbuster drugs have also come from established drug categories, where substantial sales have been won by offering modest improvements over existing products.

As pharmaceutical companies get bigger, however, the scope for one blockbuster drug to exert significant earnings leverage clearly diminishes. As a result, factors such as R&D productivity and risk-reward balance are becoming increasingly important.

- **R&D productivity** – The historical average for pharmaceutical industry R&D productivity has been just over one NCE (new chemical entity) launch per year. However, the majority of the large cap companies now target at least two to three NCE launches per annum. Very few companies are so far achieving this. A crude measure of R&D productivity can be gauged by looking at the number of drugs in development in light of their projected launch dates. Bear in mind that the risk of failure increases significantly the further the drug is from the market.

- **Risk-reward** – Ideally, an R&D pipeline should have a good balance between innovative products with high market potential but which have a higher-than-average chance of failure, and products that act by established mechanisms of action (often called me-too drugs), where the chance of failure is reduced, but where market potential may be more limited due to existing competition. A company whose entire pipeline is built on innovative mechanisms is at significant risk of bringing nothing to market.
- **Balance** – To ensure a steady flow of new drugs to the market a pipeline, a company should ideally have drugs in all stages of clinical trials. The optimal structure is pyramidal, with more drugs in Phase I than in Phase II and more drugs in Phase II than Phase III. This reflects the risk of new drug failure, which is currently estimated by consultants at nine out of ten in Phase I, six out of ten in Phase II and five to six out of ten in Phase III. As discussed above, the more innovative the product, the higher the risk of failure. Not surprisingly, a company with a 'pipeline gap', with no products in Phase III trials, is a cause for concern, as it may suggest a higher-than-average rate of new drug failure.
- **Pipeline potential** – Analysts generally estimate peak sales for each product in a company's pipeline. This usually represents forecast annual sales five years from launch. For a drug intended for use in a disease where there is already a well-established market, estimated potential is most likely to be based on a target market share. This would obviously reflect potential advantages of the new drug over the competition, but should also take into account the marketing strength of the originating company. For a drug targeted at a disease for which there is little or no existing competition, market potential would be estimated by going back to first principals in terms of patient numbers, likely penetration rate and estimated price. In general, the smaller patient numbers and the more serious the disease, the higher the price of the drug. Also worth bearing in mind is that drugs predominantly prescribed by hospital doctors would tend to require lower marketing spending than those targeted at a primary care audience. When adding estimates for pipeline products to a company earnings model, we would recommend risk-adjusting sales potential to reflect the risk of R&D failure.

Clinical terms

So, you've made the mistake of trying to read a clinical trial. What do all those ridiculous expressions mean? Here's a brief summary:

Placebo: An inactive agent or 'sugar pill' given to the trial candidate in the place of the active drug.

Double Blinded: Neither patient nor physician is aware which of the patient groups is receiving placebo and which is receiving the active drug.

Single Blinded: The patient is unaware but the physician is aware which patient is receiving placebo and which is receiving the active drug.

Open (Unblinded) Trial: Both patient and physician know who is taking drug or placebo.

Control: The reference arm of a clinical trial. It may use a placebo or, in some cases, an active drug already approved and widely used for the relevant indication.

Cross-over: The patient groups alternate treatment through the course of the trial, that is, one half take the active and the other placebo/control, and at a set time they all swap or cross over.

Randomised: Each patient enrolled in a trial has an equal likelihood of being assigned to any given treatment arm regardless of their gender, race, age, disease status, etc.

Intention to Treat: Every patient initially involved in the trial is registered in the final analysis, including those who withdrew for whatever reason. More robust than 'as treated'.

As Treated: Only the patients who completed treatment are included in the final analysis of clinical data.

Primary End Point: The primary and most important objective of the study, on which the success of the study will usually be determined.

Secondary End Point: Other objectives of the study but not those that are the key measurement.

p-Values: A statistician's term, measuring whether an outcome is statistically significant. The lower the p-value the greater the significance. A p-value of $p>0.05$ suggests limited statistical significance, while one of $p<0.01$ is highly significant.

Non-statistical: Exactly what it says….

Patient Arms: Trials often split patients into a series of arms, each receiving different doses, for example. Thus a trial of 1,000 people may have four arms, with 250 patients in each.

Markers: Typically, components in blood that are measured to give an indication of the impact of treatment, for example, number of copies of a virus found in the blood (or viral load).

Genomics & Biotechnology

The sequencing of the human genome heralds the start of an era of great opportunity and offers the drugs industry huge potential to better understand the body's workings and the basis of disease, together with the potential for an unprecedented increase in drug targets. As our understanding of our own genetic code improves and the roles of the molecules encoded by it become better understood, so our ability to rationally design new drugs specific to different individuals and new receptor targets should grow exponentially.

The Genome. What is it?

Genomics is the study of the genome and the human genome is, in effect, our book of life. It contains the instructions for the production of all the thousands of molecules that govern cell chemical activity. Our genetic code is comprised of a specific sequence of molecules called deoxyribonucleic acid or DNA, which take the form of a double helix comprised of two intertwining and complementary strands of genetic instructions.

Deoxyribonucleic Acid or DNA

Each DNA strand consists of a linear arrangement of linked and repeating sub-units called nucleotides. These nucleotides are based on only four different molecules (known as nitrogenous bases). The four are called adenine (A), thymine (T), cytosine (C) and guanine (G). Each base on one strand of DNA is linked to a specific base on its complimentary strand, forming base pairs. Importantly, strict rules are adhered to, such that A always bonds with T, and C with G. The limited number of bases and fixed nature of pairing hugely reduces the scope for error, yet maximises diversity. In total, the human genome comprises roughly 3.1 billion base pairs.

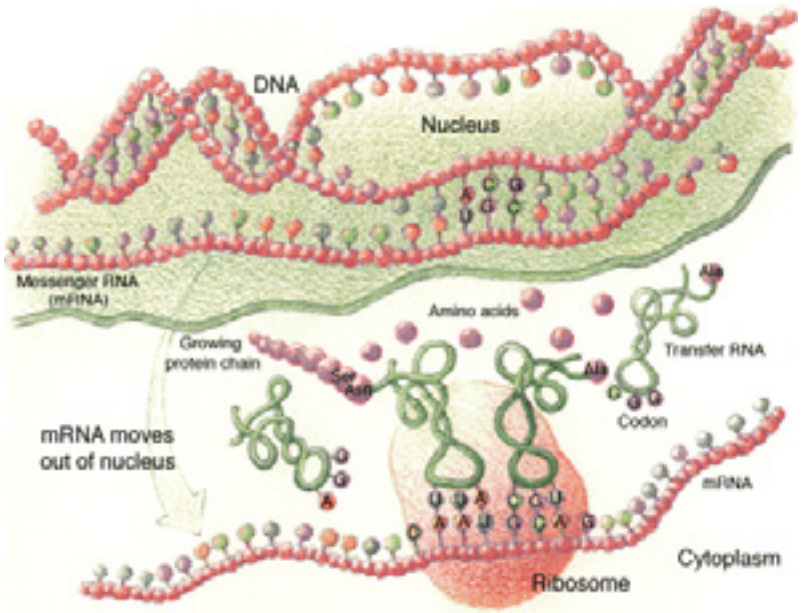
DNA is Paired in 23 Chromosomes

Within the human cell nucleus, DNA strands are distributed across 23 pairs of chromosomes (46 in total). Arranged linearly along these are an estimated 100,000 genes. A gene is a specific sequence of nucleotides that direct protein synthesis. They may vary widely in length and, interspersed within and around them on the DNA strand, are 'junk regions' that have no known coding function. Interestingly, of the 3.1 billion base pairs only 10% are thought to contain genes.

SNIPS and Polymorphisms

Each of us has 23 pairs of chromosomes. However, within each of us the exact make up of our individual DNA is not identical. Minor variations in our genes exist and it is these differences that are responsible for our individuality. If all of our DNA were identical, then we too would all be identical – one huge family of clones, indistinguishable from one another. These minor variations are known as polymorphisms (many forms). They are often benign but some variations are associated with a higher risk of disease. For example, as a result of polymorphisms, some people may be more likely to develop diabetes or Alzheimer's. Equally, differences in our genetic make-up may determine whether or not we react poorly to a particular drug. Because most polymorphisms involve only a change in one nucleotide of the DNA strand, they are often referred to as single nucleotide polymorphisms (SNPs or 'snips'). Those subsets of individuals who have a similar SNP are said to be of the same genotype.

Figure 54: The creation of proteins from DNA



Source: Human Genome Project, DoE

Gene Expression

Genes do not act independently. Rather, so-called control regions - specific sequences located within 'junk' DNA, regulate them. In effect, it is the activity of these regions that will turn a gene on or off and determine the nature of the cell's activity. This allows for functional differentiation between cells, despite the fact that each cell, no matter where in the body it is, contains the same total instruction book. Thus, a liver cell produces liver enzymes, while a pancreatic cell produces molecules specific to the pancreas, and so on. The term 'gene expression' refers to whether a gene is turned on (expressed) or not.

The process by which a gene synthesises a single protein (gene expression) is based on interpretation of the sequence of its base pairs. A gene's coding sequence is comprised of triplets of the nucleotides A,T,C and G called 'codons'. Each of the codons encrypts for one of twenty particular amino acids and the number and order of codons along a gene sequence determines the specific amino acid sequence that makes up a protein chain. Thus, codons are akin to instructions for words, which are ordered together along a gene and are read to make up a sentence (the protein). However, to continue the analogy, inserting the punctuation marks is often dependent upon instructions from other genes. This all adds to the complication of unravelling the meaning of it all.

How is the gene read?

In order for codons to be read and proteins formed, the gene's twisted DNA strands unwind and serve as a template. Within the cell nucleus a complementary strand of what is called messenger ribonucleic acid or mRNA is produced, using the DNA template. The transcribed mRNA molecule is nearly the same as the original DNA, except that a nucleotide called uracil (U) takes the place of thymine (T). The mRNA strand then moves out of the cell's nucleus and into the surrounding fluid or cytoplasm. Here it attaches to a cell constituent called a ribosome and is translated, the ribosome reading the mRNA and adding the encoded amino acids to one another to create a protein. This chain of amino acids, or protein, is then either immediately functional or will undergo further change through the influence of other gene-encoded proteins to gain its functionality.

Where are we in the Genomics Revolution?

Today, we are still at the very start of the genomic era. The sequencing of the human genome is the first step along a very long road to understanding the basic make-up of our chemistry. To date, we know the sequence of the 3.1 billion base pairs, but little about what they encode for and where the different coding sequences, or genes, are located. Equally, we have only limited knowledge of how different genes interact. Even more bewilderingly, genes encode for proteins and it these proteins that are the main perpetrators of functionality in both diseased and healthy pathways. Thus, if we are truly to benefit from our understanding of genes, we must understand the actions of the million plus proteins which they encode – how they are synthesised and how they interact. Indeed, for the pharmaceutical industry, it is proteins that represent the most likely drug targets. Consequently, it is the study and understanding of proteins (termed proteomics) that, more likely than not, will be the real key to delivering value and drugs from our knowledge of the human genome and its workings.

Pharmacogenomics

However, our increasing knowledge of the genome is already bearing fruit through pharmacogenomics. Pharmacogenomics is the study of genotype and its relationship to drug action. It is about using the right drug on the right person. It is about why some patients react favourably to drug treatment and others adversely - the answer to which is increasingly believed to be genetic. Thus, a drug such as Roche/Genentech's cancer treatment, Herceptin, is only directed at those patients who express the HER2 gene and receptor.

As said earlier, there is a long way to travel. However, the potential of our developing understanding of genomics and proteomics is huge.

- By studying the disease genotypes we should be able to predict which individuals have a predisposition to disease.
- Equally, we may be better placed to determine which groups of individuals or genotypes have a predisposition to react adversely to particular drugs.
- Disease genotypes may also reveal on which chromosome the gene associated with a particular illness is encoded.
- If we know where bad genes are located, we may be able to repair them using so called 'antisense' technology
- If we know where healthy and unhealthy genes are located, we may be able to determine the difference in the proteins that each produces and so develop appropriate drugs.
- If we understand how genes are expressed, we may be able to turn good genes on and bad genes off
- If …

…… the list is endless.

Biotechnology

Biotechnology is, in essence, man's use of the cell's chemistry to produce therapeutically useful proteins. In large part, biotechnology seeks to industrialise and manipulate chemical reactions that occur at the cellular level and produce significant quantities of structurally complex molecules.

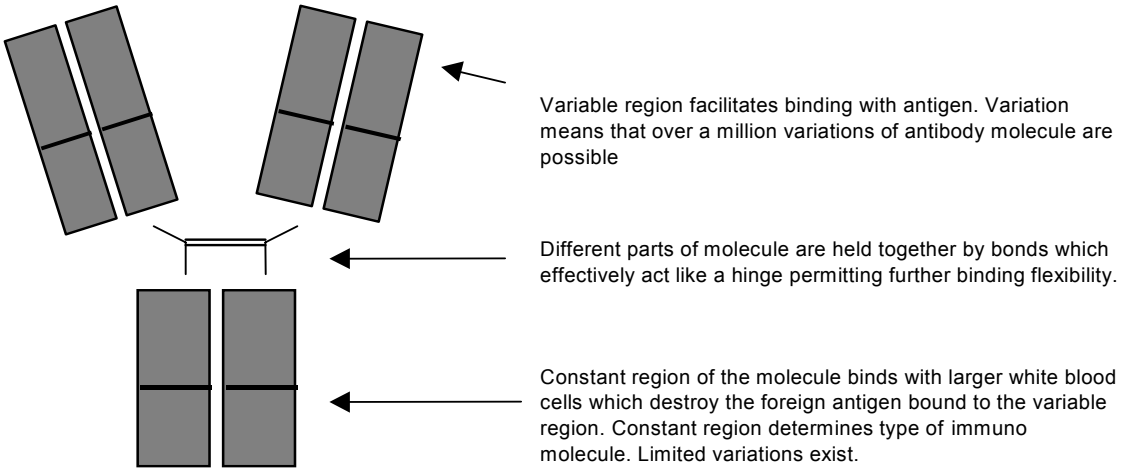
The use of biotechnology is not new. For thousands of years, man has taken advantage of the chemistry of micro-organisms to produce desirable products. For example, at its simplest level, the process of yeast fermentation represents a good example of using biotechnology to undertake an industrial-scale biotechnology-based reaction. Here, a type of fungus called yeast is fed sugar and other ingredients, which it metabolises to produce alcohol and carbon dioxide, etc.

Monoclonal antibodies (mAbs)

From a pharmacological perspective, the biotech industry really exploded in the late 1970s and early 1980s as scientists developed techniques that could isolate genes that encoded for specific proteins and recombine them in the genetic material (DNA) of cells that divided rapidly. By doing so, a desired protein could, in theory, be reproduced in commercial quantities – with the recombinant gene encoding for the desired protein and the cancer cell ensuring its rapid and ongoing replication.

Most significant was the discovery by Kohler and Milstein in 1975 – that by fusing an antibody-producing white blood cell (or B lymphocyte) with a mouse-derived cancer cell, a hybrid cell capable of mass production of a single specific antibody (a monoclonal antibody or mAb) was possible. (An antibody is a protein that is created by the host's immune system in response to a foreign particle called an antigen). This was seen to have particular relevance in the treatment of cancer, but also in other ailments where a specific protein was targeted. The theory was simple. For example, if antibodies specific to types of cancer cell could be produced in commercial quantities, then target-specific drugs could be developed. The antibody produced through genetic recombination could subsequently be manipulated to incorporate a cell toxin, e.g. a radioisotope. This could then be administered to the cancer patient and would kill the cancer cells to which the antibodies attached, but leave healthy cells intact.

Figure 55: Simplified structure of an antibody molecule


Variable region facilitates binding with antigen. Variation means that over a million variations of antibody molecule are possible
Different parts of molecule are held together by bonds which effectively act like a hinge permitting further binding flexibility.
Constant region of the molecule binds with larger white blood cells which destroy the foreign antigen bound to the variable region. Constant region determines type of immuno molecule. Limited variations exist.

Source: Deutsche Bank

Mammals can produce millions of different antibodies

Man's (or mammals') ability to produce a huge diversity of antibodies lies at the heart of his immune system and, in order to better understand antibody technology itself and some of the products in development, it is useful to have a better understanding of their structure and diversity. Antibodies take the form of a pincer-type molecule comprising four main regions (see Figure 55). Three of these are broadly constant in their structure and amino acid sequence, while the fourth sequence exhibits intense diversity. As a consequence, mammals can produce over 100 million different antibody variations. The constant regions determine the function of the antibody (e.g. whether it is raised in response to a parasite or an allergen) and facilitate binding with the white blood cells of the immune system that ultimately destroy the foreign antigen. The variable region is the part that effectively adheres to the antigen. Because so many variations are possible, given time, the body's immune system invariably develops an antibody to almost any disease and, once that antibody is created, it is mass-produced by the body until all the antigens are destroyed.

Figure 56: Monoclonal antibodies – Commercial and in development

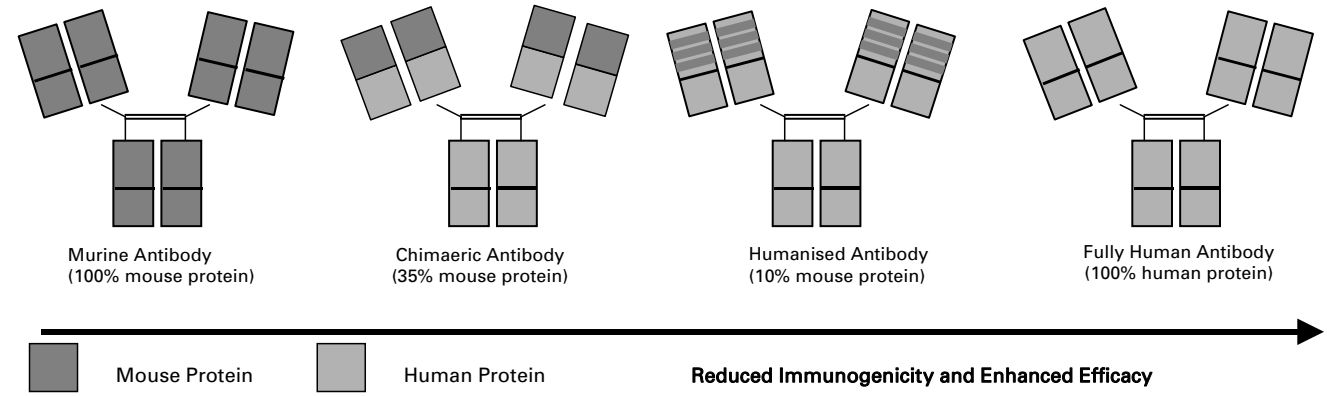
Murine	Chimaeric	Humanised	Fully human
Panorex (GSK)	Remicade (Centocor)	Herceptin (Genentech/Roche)	Humira (CAT/Abbott)
Bexxar (GSK)	ReoPro (Lilly)	Avastin (Genentech/Roche)	MDX-010 (Medarex)
Theragyn (Antisoma)	Rituxan (Roche/Genentech)	Campath (Schering)	Panitumumab (Abgenix/AMGN)
OrthoClone (J&J)	Erbitux (BMS/ImClone)	Zenapax (Genentech/Roche)	

Source: Company data, Deutsche Bank

Great in theory, but not so easy in practice

From a commercial viewpoint, production of effective monoclonal antibodies has proven very challenging. This is because all the antibodies produced industrially incorporated some amount of mouse (or murine) protein. When injected into humans, this foreign protein elicits an immune response and is destroyed. Over the years, scientists have gradually been able to reduce the amount of mouse antibody in any monoclonal. With the advent of new technologies, such as phage display and transgenic mice, scientists are now able to produce antibodies which are fully human. Figure 56 lists some of the main monoclonals in commercial production/development analysed by antibody type.

Figure 57: Evolution of antibodies from 100% mouse to 100% humanised

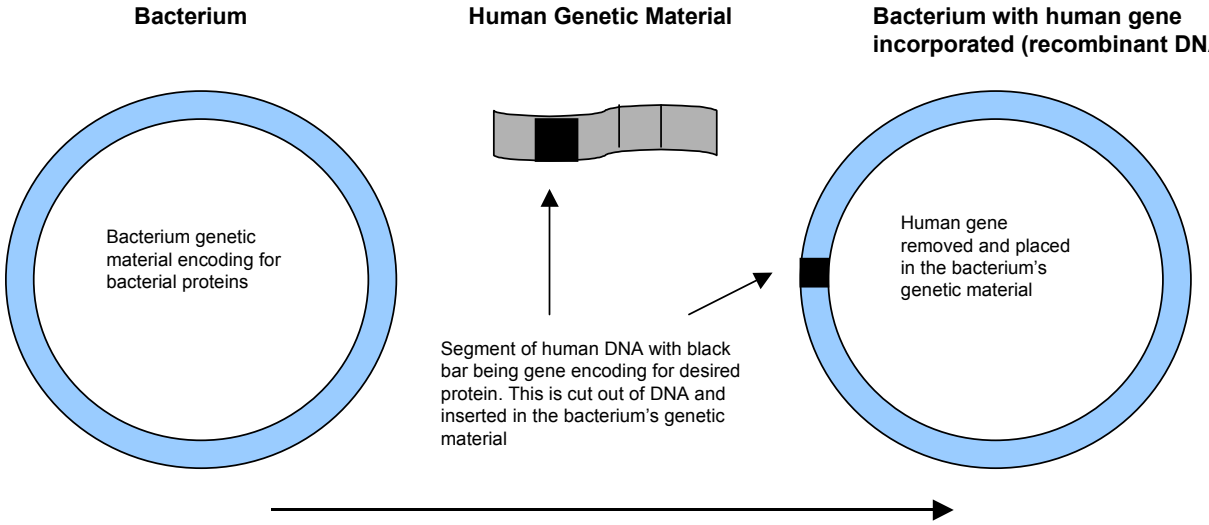


Source: Wood Mackenzie, Deutsche Bank

Recombinant technologies

Beyond the use of biotechnology to produce molecule-specific drugs, biotechnology also finds important application in the production of essential human proteins, for example, insulin and the blood-clotting activators, Factors VII and VIII. Put very basically, the concept here is simply to discover the gene responsible for the production of the particular protein and to insert that gene (recombine it) in rapidly dividing cells, typically a bacterium of some kind. The cells would then produce the relevant protein (say, insulin) which could be extracted, purified and used therapeutically.

Figure 58: Simple diagram depicting recombinant theory


Bacterium
Human Genetic Material
Bacterium with human gene incorporated (recombinant DNA)
Bacterium genetic material encoding for bacterial proteins
Segment of human DNA with black bar being gene encoding for desired protein. This is cut out of DNA and inserted in the bacterium's genetic material
Human gene removed and placed in the bacterium's genetic material

Simplified diagram illustrating basics of recombinant technology whereby a desired gene which codes for a specific protein is cut from the genetic material of one organism (say man) and inserted in the genetic material of a rapidly dividing cell. By combining the desired protein encoding gene in the genetic material of a rapidly replicating simple organism the relevant protein can be mass produced.

Source: Deutsche Bank

The regulatory process

To date, regulators globally have not created a single harmonised protocol for drug approval. As such, separate regulatory bodies and approval processes exist in each of the major markets of the US, Europe and Japan. While future harmonisation is an objective (and a process, with this as an aim, entitled the International Conference for Harmonisation, or ICH, is ongoing), as things stand today, a new drug will need to go through at least three separate approval processes if it is to be launched in the world's three largest markets. This is clearly both costly and time consuming. The requirements of the different regulators also mean that companies often have to undertake further clinical trials in order to meet the regulatory needs of the authorities in the different territories, a feature that further increases the already substantial costs of the regulatory process. Having said this, the actual filing requirements across the three regulatory regimes discussed here are gradually converging. However, one major difference between attaining marketing approval in the US as compared to other countries, is the need to agree on pricing with the authorities in both Japan and Europe. This often leads to significant delays between actual approval and product launch.

Regulation in the US

As with drug development, the process of regulatory approval in the US falls under the supervision of the Food & Drug Administration (FDA). A new drug sponsor (invariably the drug manufacturer) will submit a file, called a New Drug Application (NDA), for a new chemical entity (NCE) to the FDA for approval to manufacture, distribute and market the drug in the US, based on the data collated through the clinical trial process. This file comprises a multitude of information, including written reports of each individual study, manufacturing data and a summary of all available information received from any source concerning the safety and efficacy of the drug. Included in this must be at least two pivotal trials, one of which must have been undertaken in the US (pivotal trials represent the key clinical trials confirming efficacy and so on for any NCE submission). In addition, 120 days prior to a drug's anticipated approval, the sponsor must provide the FDA with a summary of all safety information surrounding the new drug, including any additional safety data obtained from trials undertaken during the review process.

Advisory committees

Following NDA submission, the FDA has 60 days to inform the sponsor that the application is complete and worthy of review. At this stage, the FDA designates the review track for the product. Today, the standard review process is 10 months. In the case of a therapeutic breakthrough, a drug may be granted an 'expedited' six-month review. Assuming FDA acceptance, the submitted NDA will be forwarded to a specialist therapeutic department, the bias of which depends on the drug. For example, a cancer treatment will be forwarded to the Division of Oncology and so on. The FDA also frequently seeks advice from its 17 standing advisory committees on drugs, particularly on NCEs. These comprise independent scientific experts, physician researchers and statisticians who will make a recommendation to the FDA as to whether an NDA should be approved or not. The FDA is not, however, obliged to heed their advice.

Approvable, approved and complete review

Assuming that the NDA meets the efficacy and safety requirements of the FDA, if there are no outstanding issues, a drug may be granted an immediate approval at the end of the formal review process. However, often, if there are outstanding labelling issues, or if the FDA has requested additional clinical trial data, a drug will be deemed 'approvable', with formal approval following some months later, once the outstanding issues are resolved. Formal

approval by the FDA typically follows about one to three months later, following discussions on the prescribing label and, once received, the drug may be launched.

Importantly, the FDA has recently indicated that it intends to replace both 'approvable' and 'not-approvable' letters with 'complete review' letters. As such, visibility on the nature of the FDA's response to a drug NDA looks set to become more dependent upon the disclosure made by the drug sponsor. Letters issued will, as before, detail deficiencies in the drug application and actions necessary for approval. These details will, however, only be available to the drug sponsor.

The drug label and black boxes

The period between receipt of an approvable or complete review letter and FDA approval itself can, however, take considerably longer. This may be because the FDA believes that further information is required, confirming safety or efficacy before launch. Alternatively, the delay may be due to a debate between the drug sponsor and the FDA on what should or should not be incorporated into the drug's label. A drug label represents the information that must be made available to consumers whenever that drug is dispensed (that sheet of paper enclosed with every drug that we usually throw away as soon as we open the packaging). Importantly, the label details all the safety data, together with any specific marketing or superiority claims permitted by the FDA (in other words, claims made following clinical trials that demonstrate the drug's superior efficacy relative to other products). In certain instances, the FDA may require that the label emphasise potential drug side effects, that is, a health warning. This might be by way of bold text or, in extreme cases (and typically if the drug can result in fatalities), the addition of a warning in a clearly visible black box. This is excitingly entitled a Black Box Warning and is clearly not conducive to sales.

The label is important to the drug company, as it determines which claims for the product can be made in marketing. Promotional claims cannot be made unless they are included in the drug's label.

ANDAs and sNDAs

Outside new drug applications (and the INDs discussed in the Research & Development section of this report), the FDA also frequently deals with two other types of drug application - supplemental new drug applications (or sNDAs) and abbreviated new drug applications (or ANDAs).

- **ANDAs**: An ANDA is the submission required for launch of a generic version of an existing approved drug. They are called abbreviated, because they are not required to include data on animal and human clinical studies. Rather, they must demonstrate that the generic dru is bioequivalent to the innovator drug. This means that the generic drug is chemically identical to the branded product and is absorbed by the patient in the same way, such that the blood concentrations of the two are identical.
- **sNDAs**: Supplemental NDAs are tghose filed for drugs that are already approved, but for which a new/additional indication is being sought (for example, the use of the anti-depressant Prozac for treatment of pre-menstrual tension). Depending on the indication, the drug company may or may not be required to submit clinical data demonstrating efficacy in this additional indication, together with additional safety data. The time frame for approval is six months if clinical data are not required, or 10 if a review of clinical data is necessary.

User fees see complete review periods shortening

Reform of the FDA over the past decade has seen a vast improvement in the time taken for regulatory approval. On average, the FDA now aims to act on 90% of standard NDAs within 10 months. Although the initial response from the FDA may be an 'approvable' letter, for example, meaning the total review time could be significantly longer, this still represents a

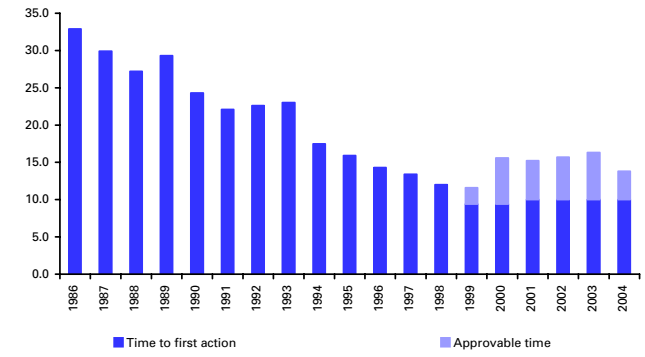
dramatic improvement on the two to three years that was typical earlier in the 1990s. In addition, the total number of drugs approved in any one year also increased, from around 20 in the early 1990s to around 30 in the late 1990s. Among other things, two pieces of legislation have driven this change.

- **The 1992 Prescription Drug User Act (PDUFA**), under which the pharmaceutical industry agreed to pay $327m in 1993-1997 to enable the FDA to hire additional reviewers, and
- **The 1997 FDA Modernisation Act (FDAMA),** which requires the FDA to promote public health by timely review of NDAs and to protect health by ensuring products are safe, effective and properly labelled. The Act also saw the pharmaceutical industry agree to pay circa $600m in user fees to facilitate a reduction in approval times, and the FDA agree to review standard NDAs in an average of ten months, from the prior average of 12 months.

User fee deadline and priority review

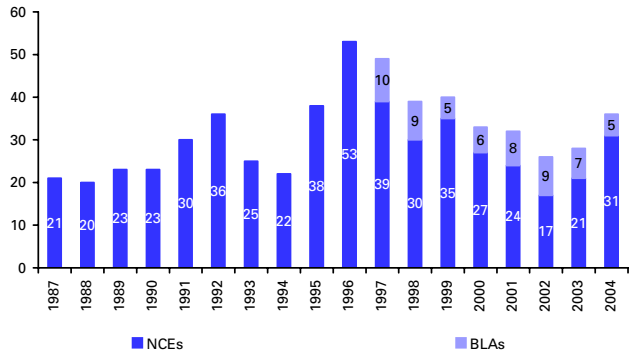
These two acts have led to the establishment of the user fee deadline. The FDA's goal from October 2002 is to respond to 90% of all standard reviews within ten months. Failure to do so means that the FDA is obliged to return the user fee – typically, several hundred thousand dollars – to the drug sponsor. However, the FDA is only obliged to deem a drug approvable or not approvable within this time period. The time to full approval may, as previously indicated, take longer if the labelling discussions are protracted, or if the FDA requests additional data. A key feature of the FDA of late has been the increase in the number of products undergoing protracted 'approvable' processes.

Figure 59: Review times 1986-2004



Source: FDA

Figure 60: NME approvals 1987-2004



Source: FDA

As previously mentioned, where a new drug application is for a product that represents a significant medical advance on existing therapies, it may be 'fast tracked' by the FDA and receive a priority review. For these priority NDAs, the FDA is committed to review and act on the application within a six-month time frame. This is clearly a major advantage for the innovator and an important incentive for undertaking innovative research in new therapeutic areas.

More recently, the FDA has introduced a further concession to speed certain priority reviews. For drugs that it deems to be of particular therapeutic benefit, data can be submitted in parts (i.e. on a rolling basis), the FDA committing to review each 'reviewable unit' within six months. Thus, the review process and feedback may start earlier, albeit the six-month clock from a PDUFA perspective will not start until the final section of the rolling filing has been submitted. A recent example of a drug application which was reviewed on a rolling basis was that of Eli Lilly's cancer treatment Alimta. It should be noted, however, that under a rolling review, a product can only be declared approved or not approved. There is no halfway house.

As a final comment, it is worth recognising that the PDUFA legislation sunsets every five years. In this way, Congress actually introduced greater flexibility to the act by enabling issues arising in the existing legislation to be tackled and funding requirements assessed within a reasonable time frame. Thus, for example, under PDUFA III, the FDA has seen a near 60% increase in its funding from the pharmaceutical industry. In return for this, however, it has committed to improving the level of dialogue with NDA sponsors through the review process and to attempt to complete the first review cycle on any NDA in sufficient time to allow for second and third reviews before the PDUFA action date. It is hoped that, given greater funding, initiatives along these lines will see a reversal of the recent decline in approval times.

Regulation in Japan

Recent years have seen the Japanese regulatory system move towards that of the US, driven in part by internal scandals, which led to strong calls for change. The previous system accentuated development and promotion of 'me-too' drugs and incorporated effective barriers to approval of drugs promoted by foreign firms. Indeed, until 1985, foreign firms were not allowed to apply without a Japanese partner for the first step of drug approval, and foreign test data were not accepted. Thus, a non-Japanese company that wished to introduce a product into the Japanese market was required to undertake duplicative clinical testing in Japan, with clinical trials conducted on native citizens. Clearly, this required significant additional investment, not to mention considerable delays in the time to launch.

Historically, approval times in Japan have been significantly longer than in Europe and the US. This appears, on occasion, to have been particularly so when a Western company has been the principal drug sponsor. Recognising this weakness, the Ministry of Health and Welfare set up the Pharmaceuticals and Medical Devices Evaluation Centre on 1 July 1997 to "strengthen the Japanese government's evaluation capacity for securing safety and preventing harmful side effects of pharmaceuticals." The Centre evaluates the quality, efficacy and safety of prescription drugs and medical devices. It also assesses proprietary drugs, quasi-drugs and cosmetics that are purchased directly by the general public.

It is also of note that until August 2002, the licence granted in Japan (i.e. the approval) was one for manufacturing of the drug rather than its marketing. As such, companies seeking approval have had to manufacture their own product, a requirement that, by restricting companies' ability to out-source production, has also led to significant inefficiencies among the Japanese manufacturers, in particular. However, following a revision in the Pharmaceutical Affairs Law (PAL) in 2002, this restriction has now been removed, the approval of a product now being approval to market.

The evaluation process for a new drug can be summarised as follows. On receipt of the New Drug Application (NDA) the Ministry of Health, Labour and Welfare (MHLW) forwards it to the Pharmaceuticals and Medical Devices Agency (PMDA), where it is assessed by a panel of experts with backgrounds in pharmaceutical science, medicine, dentistry, veterinary, bio-statistics and so on. This panel produces a scientific assessment, which is then submitted to the Central Pharmaceutical Affairs Council, a consultative body to the MHLW. Further committees can be convened to assess the application, if deemed necessary, and can request further information from the drug sponsor. Finally, the Executive Committee, which meets four times every year in January, April, July and October, issues the final approval.

MHLW has boosted assessment infrastructure to reduce approval times

Until recently, it was not unusual for three years to pass from the time of filing an NDA to final approval by the Ministry of Health and Welfare. As part of efforts to radically strengthen the system of drug assessment in 1997, the ministry began implementation of a three-year plan to double the number of NDA examiners (despite which, in 2004, still stands at around

300 compared to the 2,800 reviewers now employed by the FDA). This was part of an attempt to reduce approval times, initially to two years, but for products submitted from April 2004 onwards, the PDMA now targets a complete review of at least 70% of applications within 12 months. (In 2004, 65% of applications were reviewed in 12 months.) In addition, it is worth noting that the ministry deems an approval assessment 'live' (with the regulatory clock running) only when under active consideration. The clock is not running, if extra data requested of the NDA sponsor are awaited or while questions raised by the PDMA are being answered.

An official price is required for national health insurance reimbursement

Once approved, a drug containing a New Chemical Entity (NCE) must be granted an official price before it can be reimbursed on insurance. New Chemical Entities are added to the National Health Insurance Drug Price List four times per year (in March, May, August, and November), at prices calculated via comparison with approved drugs. Historically, comparative drugs were selected based on similar chemical structures, indications, therapeutic effects and so on. The price of the new drug was then based on the daily price of the comparable drug, with premiums added for innovation and based on market size. If no similar drug could be identified, a price was set according to the cost calculation method. Prices calculated using this method are adjusted if they are more than double or less than 50% of comparable drug prices in the US and Europe.

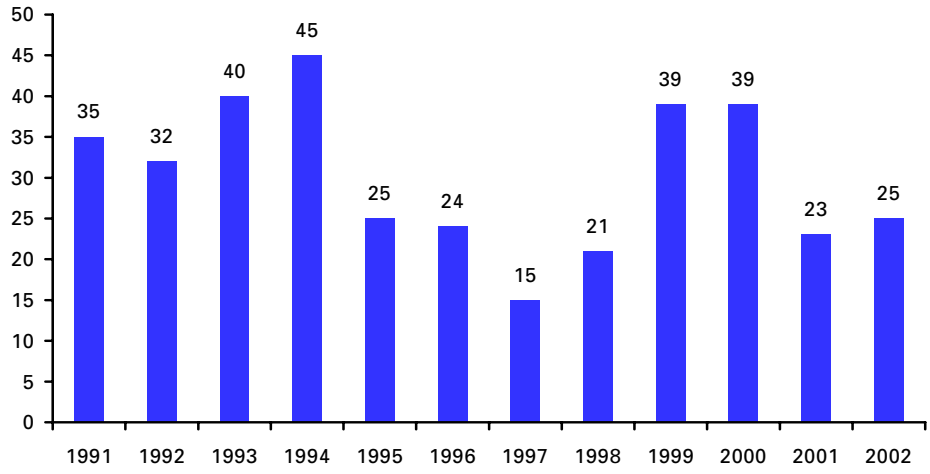
New drug pricing organisation implemented in 2000

Sadly, this system did little to reward or incentivise innovation. Thus, the MHLW implemented new administrative procedures for the pricing of pharmaceuticals in October 2000. The main change attributable to the new system is that manufacturers' pricing proposals are now considered by committees within a new Drug Pricing Organisation (DPO) after passing through the economic affairs division of the ministry's Health Policy Bureau. The DPO has 11 members, supplemented by around 30 external academic and medical experts, pharmacologists, economists, and dental sector specialists.

Under the new system, companies are able to suggest and provide relevant data on comparative products, but have to justify any price premium request. Premiums are granted taking into account the degree of innovation, limited marketability and medical usefulness. After considering the application, the DPO must reach a majority decision before passing on its proposal to the Central Social Insurance Medical Council, which provides the final ratification. An appeal process exists, whereby further written and verbal arguments can be heard if no agreement can be reached.

Once agreed, price listing should occur within 60 days of approval (90 days maximum) by the ministry's advisory Central Pharmaceutical Affairs Council. The current requirement to market listed drugs within three months remains. The DPO is expected to meet at least four times a year, although listing of essential life-saving drugs will be considered on an ad-hoc basis. The DPO will also consider re-pricing those products for which the market has significantly expanded.

Figure 61: Japanese new drug approvals 1991-2001



Source: MHLW

Bilateral trade agreements have proved a catalyst for change

These changes have been prompted, at least in part, by Japan's commitment to speeding up the approval and listing of drugs under various bilateral trade and deregulatory agreements with the US. For example, the third report of the US-Japan Enhanced Initiative on Competition and Deregulation was endorsed by President Clinton and Japanese Prime Minister Mori at the July 2000 Group of Eight (G8) summit in Okinawa, Japan. Under the initiative, Japan has undertaken to implement specific measures to improve transparency (although certain local and foreign industry groups remain dissatisfied with some aspects of the price calculation methodology) and to expedite approval procedures for drugs and medical devices. This includes the use of foreign clinical trial data and recognition of the value of innovation. As we have already seen, the adoption of ICH guidelines has helped in this regard and, since April 2000, MHLW has sought to approve new products within one year.

Generic drugs, those containing previously approved active ingredients, are price-listed annually in July. Prices for the initial listing of a generic are set at 70% of the price of the original drug, but if other generics are already listed, the price set is the same as that of the cheapest existing generic. However, if the number of newly approved products and existing generics is greater than 20, the new price will be set by multiplying the lowest price by 0.9.

Regulation in Europe

Until the mid-1990s, the medical committees of the different national European states determined regulatory approvals in European markets. Limited harmonisation existed and approval of a single medicine across Europe was often time consuming and costly. However, in 1995, a new European system for the authorisation of medicinal products came into operation with the foundation of the European Agency for the Evaluation of Medicinal Products (EMEA). The EMEA's main role is to coordinate and manage the drug approval system within Europe. The system evaluates any new product marketing application through either a centralised or a decentralised (i.e. mutual recognition) procedure. Biotechnology products have to be evaluated through the centralised procedure, whereas most new chemical entities can be evaluated either through the centralised system or via mutual recognition. However, if recent proposed changes to European regulations are approved, all drugs for cancer, HIV, neurodegenerative disorders and diabetes will need to be submitted via the centralised procedure. Approvals for generics and line extensions (additional indications) must go through the national regulatory bodies.

The EMEA comprises four bodies, one of which, the Committee for Medicinal Products for Human Use (CHMP, formerly known as the Committee for Proprietary Medicinal Products or CPMP), is responsible for formulating the EMEA's scientific opinion on marketing applications for human medicines. This regulatory committee comprises scientific experts in medicinal product evaluation, who are invariably employees of national regulatory authorities and are given responsibility for issuing an opinion on whether a new drug may be marketed to the board of the EMEA. The board then reports to the European Commission which issues marketing authorisation.

The centralised procedure

Under the centralised procedure, a new drug sponsor submits its application directly to the EMEA. The application is presented at the next monthly meeting of the CHMP and two committee members (called Rapporteurs) are appointed to co-ordinate the evaluation of the application. The national regulatory authorities of the appointed committee members then normally undertake evaluation. Once evaluation has been completed and reported to the CHMP, the CHMP will issue a scientific opinion on the product. This opinion is then conveyed to the European Commission which is authorised to convert the opinion into marketing authorisation, valid throughout the entire European Union.

EMEA guidelines are that the entire process should take no longer than 300 days. The CHMP is obliged to issue an opinion within 210 days of receipt of an acceptable dossier. However, if questions are raised during evaluation that require additional information, the clock stops until the questions are resolved. After the CHMP has issued its opinion, the EC has an additional 90 days to convert the opinion into a final decision.

Overall, the CHMP has proved very efficient in evaluating new products. Between 1995 and 1998, the average time taken before issuing an opinion on all the biotechnology products reviewed was 174 days. However, the total timeframe can prove disappointingly long. As much as anything, this is because the EMEA takes an average of 40 days to transmit the CHMP opinion to the European Commission, at which time EU member states are allowed to raise further questions. Thus, for the 1995-98 period, while the time taken for the CHMP to issue an opinion was only 174 days, time to approval was actually 305 days. This timeframe also excludes 'stop-clock' periods, which can be considerable.

Mutual recognition procedure (MRP) or decentralised procedure

Under the MRP system, an NDA is initially forwarded to one member state. If national authorisation is granted in that state, it allows for extension to one or more other member states. Under the MRP, the holder of the national authorisation for which mutual recognition is sought may then submit an application to other member states, certifying that the dossier is identical to the one for which first approval was granted (or explaining any differences). Within 90 days of receiving the application and assessment report, each member state must then decide whether to recognise approval. When such mutual recognition between member states is not possible, the EMEA will arbitrate and the European Commission issues a binding decision.

Pricing, efficacy and formularies

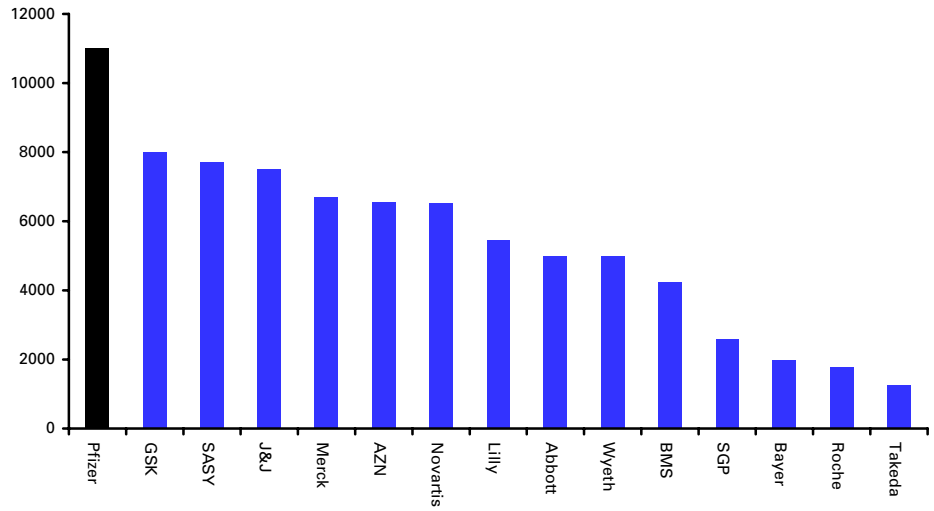
Subsequent to approval, the sponsor must then enter negotiations with the relevant national bodies over price and formulary inclusion. Time taken for this process can again be considerable. In addition, if the member state believes that the medicine does not offer value for money or a significant medicinal advance, it need not approve its inclusion on formularies and may even recommend that physicians do not prescribe it. Thus, for example, the UK's National Institute for Clinical Excellence (or NICE) recommended that GlaxoSmithKline's flu treatment Relenza was neither included on formularies nor prescribed by physicians.

Pharmaceutical marketing

The importance of marketing a new or existing drug cannot be underestimated. As the costs of drug development have increased and the time between innovator products and 'me-too' versions has shortened, so the importance of maximising revenue from any drug that passes through the clinical process has increased. Consequently, the major drug companies have recognised that a strong marketing message and rapid penetration of the potential market are vital if a drug is to attain peak sales as rapidly as possible and maximise the total revenue achievable over its patented life.

This recognition has, in recent years, seen several important developments. Sales forces in key markets, most importantly the US, have been increased, while companies have spent more on clinical trials post-launch in order to differentiate their product and strengthen the marketing message. In addition, greater emphasis has been placed on influencing key opinion leaders, such as hospital specialists, most significantly ahead of a product's launch. Above and beyond this investment, the advent of direct-to-consumer advertising in the US has seen the major drug companies invest heavily in consumer-orientated television and press advertising, as they have sought to use the ultimate consumer of drug to direct physician prescribing. Increasingly, the industry is also moving towards global launches. In other words, today, launches across the different geographic territories occur within a much narrower time frame than was the case historically. This has been helped by the gradual harmonisation of the regulatory process in the markets of Europe, the US and Japan.

Figure 62: Ranking of companies by US sales force size in 2004



*Source: Company data, *Includes Pharmacia*

Targeting decision makers, not buyers

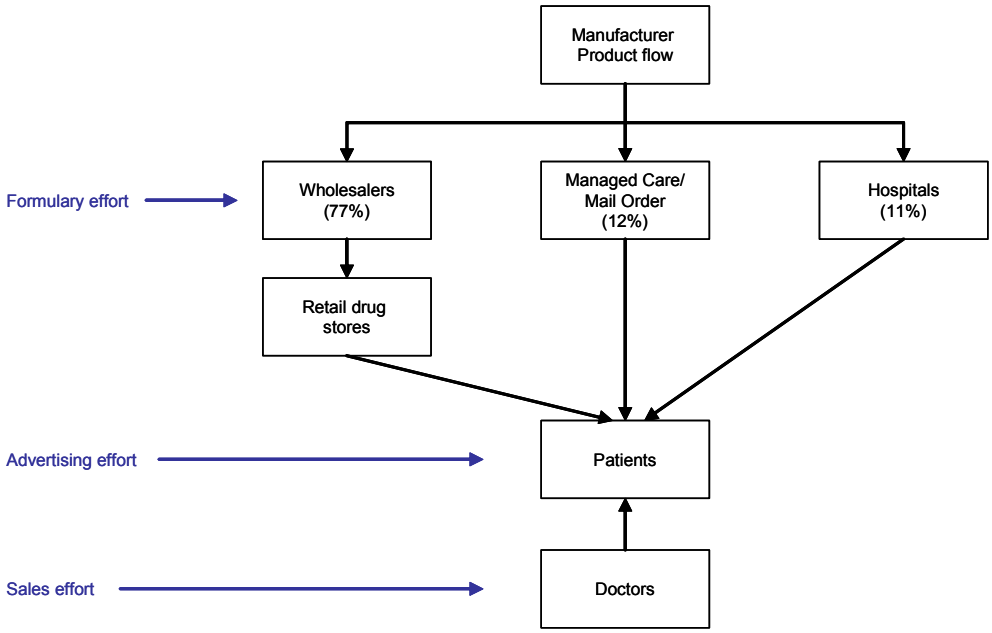
Importantly, it needs to be appreciated that pharmaceutical markets are different to many other markets, in that the selling effort is, in the main, not targeted at the actual buyers of drug. Rather, it is targeted at the decision-makers in the process with a view to influencing their prescribing patterns. Thus, the bulk of any drug company's sales and marketing effort is directed at the general practitioners, consultants and hospital specialists who determine which medicine a patient should take, rather than the government, managed care organisations or private healthcare groups that actually pay for the drugs. Of course, the companies have relationships with these buyers. The focus here is, however, invariably to

ensure that the drug is included on the buyer's reimbursement formulary. Often, this will come down to convincing the relevant authority that the economics make sense, i.e. it is cheaper to prescribe the new drug than to face later hospitalisation costs or time lost at work due to ilness.

Retail or hospital?

The pharmaceutical company's approach to marketing will also differ depending upon whether the drug is to be used in the hospital or prescribed through a physician's practice (sold through retail pharmacies). Because the hospital market is smaller and more concentrated, the absolute size of the selling effort required is, as a rule, considerably less. Hospital sales forces are typically smaller than those marketing to general practitioners. In addition, because the hospital market tends to be more specialised, drugs used in the hospital environment may achieve more modest sales than those aimed at the mass retail market. The exceptions are biological products such as the erythropoietins and targeted cancer therapies, which due to their high cost, can often achieve multi-billions in sales.

Figure 63: US drug routes to market and manufacturer sales efforts



Source: Deutsche Bank

Drug lifecycles

Crudely, the lifecycle of a drug can be broken down into five phases: pre-launch, launch/growth, extension, maturity and patent expiry.

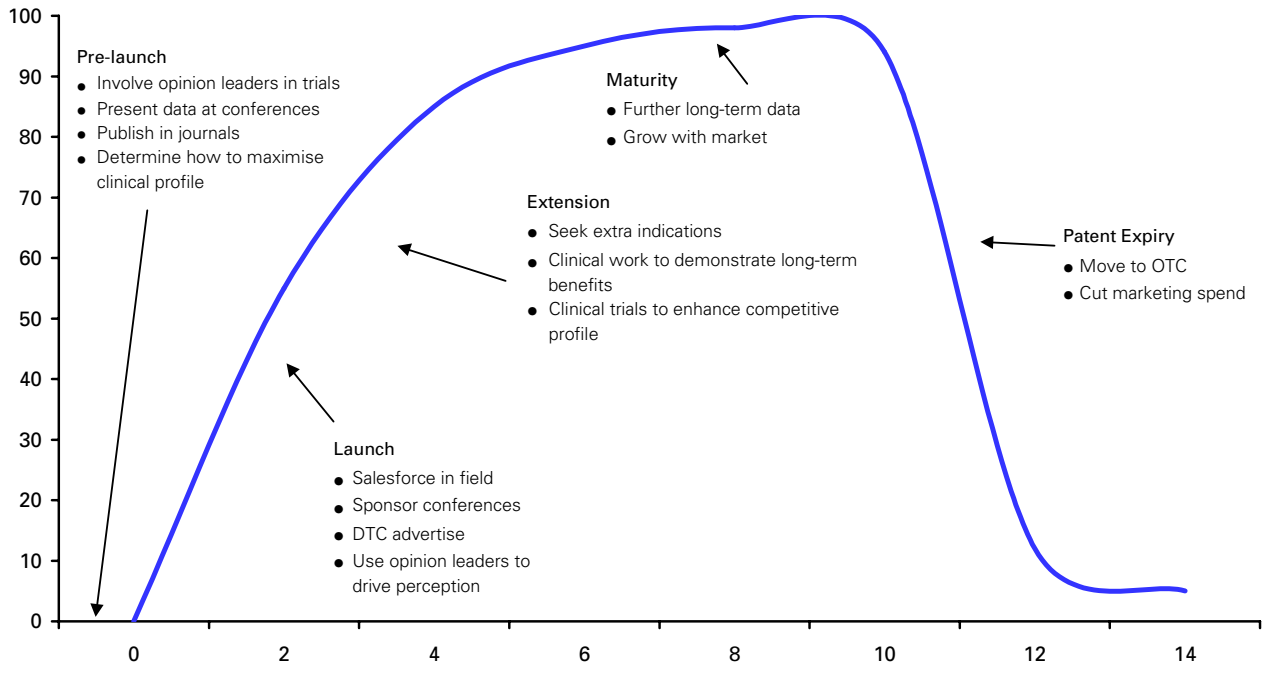
Pre-launch: The pre-launch phase encompasses the work that is undertaken to prepare the market for the new drug while it is still going through the clinical trial and registration process. Simplistically, it can be broken down into events that occur internally or externally.

- Internally, it involves liaison between marketing and research to create a clinical data package that will position the drug as favourably as possible in the market. In other words, it seeks to design trials that will maximise the drug's attributes and position the drug as favourably as possible in the eyes of the medical fraternity and patients. Using these data, and with the requirements of the market in mind, the marketing department will seek to create a clear and simple message of what the drug is and why it should be used.

- Externally, pre-launch initiatives involve attempting to ensure that key opinion leaders in the relevant field will promote the drug through the medical community. While the actual marketing of an unapproved entity is prohibited by the regulators, much can be done to increase market awareness and ensure that those with influence are exposed to the new drug ahead of launch. Efforts here include getting experts in the field to oversee clinical trials, presenting clinical data at conferences to increase awareness, publishing clinical findings in leading journals and, in general, creating as much awareness within the medical fraternity as possible of the potential benefits of the treatment in development.

Launch/Growth: The growth phase involves the all-important launch of the drug for its lead indication. Having seeded the market for the launch, during launch itself, the company will focus on maximising patient and physician awareness. Here, the scale and effectiveness of the salesforce is absolutely key and contract sales representatives may be used to further leverage the efforts of the company's own sales representatives. Out in the field, the salesforce will seek to inform as many physicians of the drug's release as possible, providing them with free samples for patient use and extolling the new drug's virtues. Managed care organisations will also be heavily targeted as the pharma company seeks to ensure that the new drug is included on formularies. The company will finance conferences and seminars at which key opinion leaders will speak, as it seeks to disseminate information throughout the market. Key opinion leaders will also be encouraged to host small seminars for other physicians, at which the disease and its treatment with the new medication will be discussed, while many pharmacists will be contacted and made aware of the drug's release. Some months into the launch, direct-to-consumer advertising may also be employed to drive consumer awareness.

Figure 64: Schematic of the lifecycle of a drug



Source: Company data, Deutsche Bank

Extensions: The extension phase in the lifecycle of a new drug broadly involves obtaining new treatment indications and enhancing the competitive profile of the drug.

- **Line extensions/additional indications**. Most drugs can be used for more than one disease. For example, schizophrenia drugs also find use in biopolar disorder, while cancer drugs may be used for more than one type of cancer. Thus, the extension phase in the lifecycle of a drug involves seeking additional applications for the medicine and gaining approval for its use in these new indications. The effect is to broaden the drug's total market opportunity.
- **Competitive profile**: Throughout the life of the drug, most companies will also look to sharpen the drug's clinical data package and competitive profile. Further clinical trials will be undertaken with a view to showing the long-term benefits of treatment or to demonstrate that it is more efficacious than other class competitors. With the approval of the regulatory bodies, data collected from these trials can then be included on the drug's label and used as additional promotional messages.

Maturity: Efforts to extend a drug's range of indications and its competitive profile may continue for much of the drug's life. However, through its later years of patent protection, growth will largely reflect that of the underlying market. Investment and marketing spend will start to tail off and the drug innovator will most likely view the mature drug as a cash cow.

Patent expiry: Following patent expiry, revenues may fall sharply depending on whether generics enter the market or not, and clinical and marketing investment will be largely withdrawn. Depending on the nature of the product, the drug company may seek to gain approval to sell the drug over the counter (OTC), i.e. as a branded non-prescription medicine. In addition, several firms have recently introduced their own 'authorised' generic products following patent expiry in order to retain a modest fraction of their former revenues.

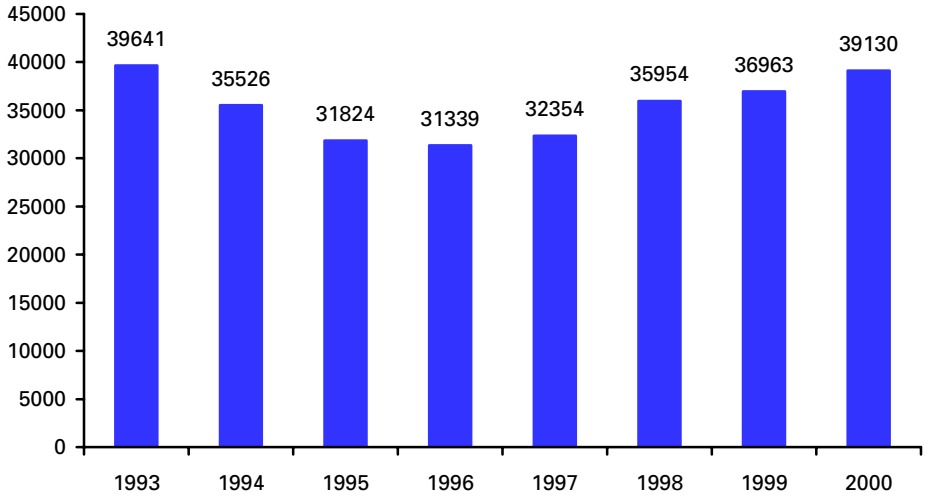
Salesforce size

Recent years have shown that one of the keys to a successful launch and overall presence in the market place is the strength of the company's salesforce. The past ten years have seen a major shift in companies' attitudes towards the role of sales representatives in the all-important US market. In the early to mid-1990s, the growth in importance of the managed care organisations as providers of health coverage led to the view that these organisations would increasingly dictate which drugs would be prescribed by physicians. As such, the industry believed that less time needed to be spent on detailing physicians and more on the less labour-intensive and larger managed care groups. The result was a reduction in salesforce sizes. However, in the event, although the managed care organisations established drug formularies (albeit not very restrictive), the physician remained the predominant decision-maker. Consequently, penetration of the physician base has proven absolutely vital if a drug is to achieve its potential.

Indeed, recent years have demonstrated that US salesforces play a key role in determining whether or not a product will prove successful. Time and time again, under-representation in the US market has resulted in drugs failing to achieve their potential, despite encouraging clinical profiles (witness Bayer's Avelox, AstraZeneca's Accolate or Akzo's Remeron). And, as the absolute size of the major companies' salesforces increases, so the bar is being raised.

Concentration of the selling resources on key products is also of great importance. In itself, absolute size means little. What is important is the weight of effort that goes behind a particular drug. In other words, a sales force of 5,000 promoting 30 products is of less value than one promoting ten. The consequence of this has been the decision by many of the majors to allocate a substantial proportion of their total sales effort to a handful of those drugs that have blockbuster sales potential.

Figure 65: Total US physician calls 1993-2000



Source: IMS Health

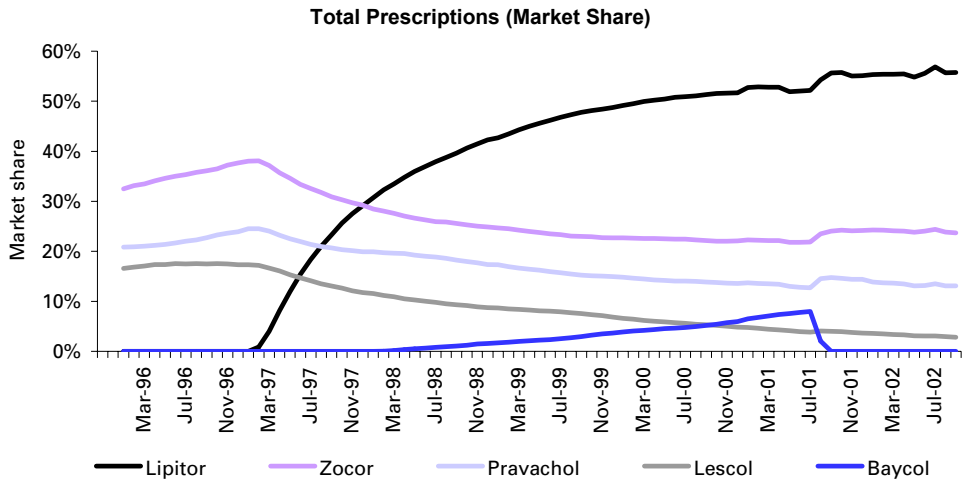
There is, of course, another benefit to salesforce size. The stronger a company's sales representation, the greater its attractions as a co-marketer of choice for products emerging from smaller companies' pipelines. This point has been well demonstrated by the phenomenal success of Pfizer's co-marketing arrangements with Eisai for Aricept, Boehringer Ingelheim for Spiriva, and prior to its eventual outright purchase, Warner-Lambert for Lipitor and Pharmacia for Celebrex.

Drug profiles

As therapeutic markets have become more competitive and marketing more important, so drug manufacturers have invested more in trying to differentiate their products and provide their salesforce with a clear marketing message. For any drug, high efficacy, a favourable side-effect profile and a convenient dosing schedule that favours compliance (i.e. oral, once a day) will always prove points in its favour. However, to the extent that the drug company can build on these claims by undertaking further clinical work to broaden a drug's range of indications or demonstrate superiority vis-à-vis other class competitors, the marketing message can be enhanced. New claims can also serve to re-invigorate the drug salesforce, providing them with a new message to market to physicians.

The importance of a drug's profile and the impact it can have on performance are well illustrated by the phenomenal success of Pfizer's cholesterol-lowering drug, Lipitor. Despite being the fifth drug of its type to market, Lipitor's superior profile combined with Pfizer's marketing muscle resulted in one of the most spectacular launches in the industry's history. By contrast, the result of getting the profile wrong, by misreading the market and not putting sufficient sales resources behind a drug was illustrated by Bayer's early experience in the same market with its cholesterol lowerer Baycol (which was subsequently withdrawn following deaths associated with a later introduction of a higher dose). Despite being priced at only 80% of Lipitor's level, prescriptions for Baycol were disappointing, as the company mistakenly considered that price rather than efficacy would drive market share.

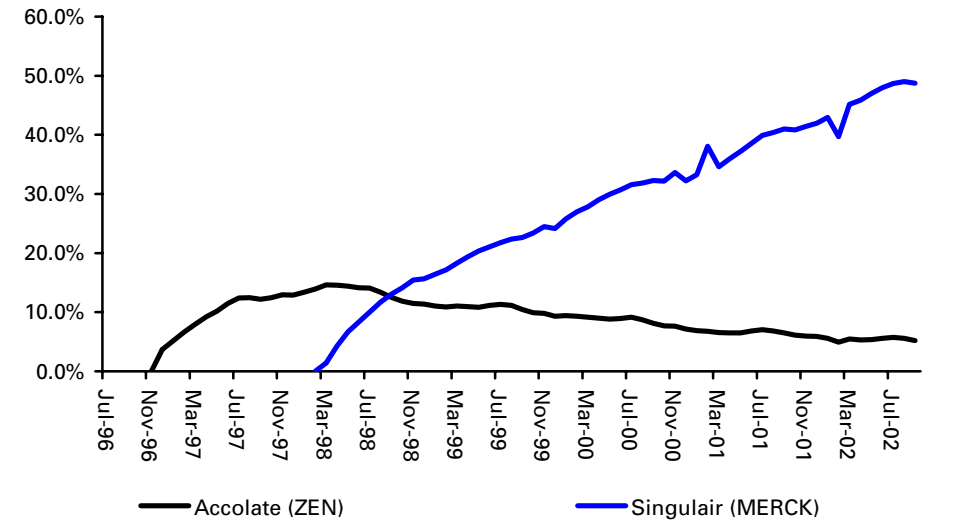
Figure 66: Cholesterol-lowering US market shares 1996-2002



Source: IMS Health

Similarly, the performance of AstraZeneca's Accolate against that of Merck's Singulair demonstrates how marketing savvy can lead to excellent results. While both products have similar profiles, Merck has completely outgunned its smaller UK competitor, despite being second to market, with a clearer and more distinct marketing message. The profiles also demonstrate physicians' clear preference for a once-a-day formulation - Singulair is taken once a day against twice a day for Accolate.

Figure 67: Leukotriene antagonist US market shares (1996-2002)



Source: IMS Health

Direct-to-consumer advertising

Beyond the use of salesforces to increase physician awareness, liberalisation of the restrictions on television advertising of drugs in the US has seen the major companies target consumers directly in order to increase brand and, indeed, disease awareness. This has proven particularly true for those drugs used to treat so-called life-style disorders (e.g. impotence or hair loss), but also drugs for diseases where the consumer may influence the

physician's decision, such as allergy, as illustrated in Figure 68. This details the top ten DTC products advertised in 2004.

DTC advertising places advertisements of prescription drugs in magazines, on television, on radio and, more recently, on the Internet. It has been legalised in the US, but not in Europe or Japan. However, it is worth noting that DTC advertising can reach consumers in these regions through the 'back door' via the Internet, as drug manufacturers' sites do not block access to those requesting information from outside the US.

Figure 68: DTC spending 2004 ($m)

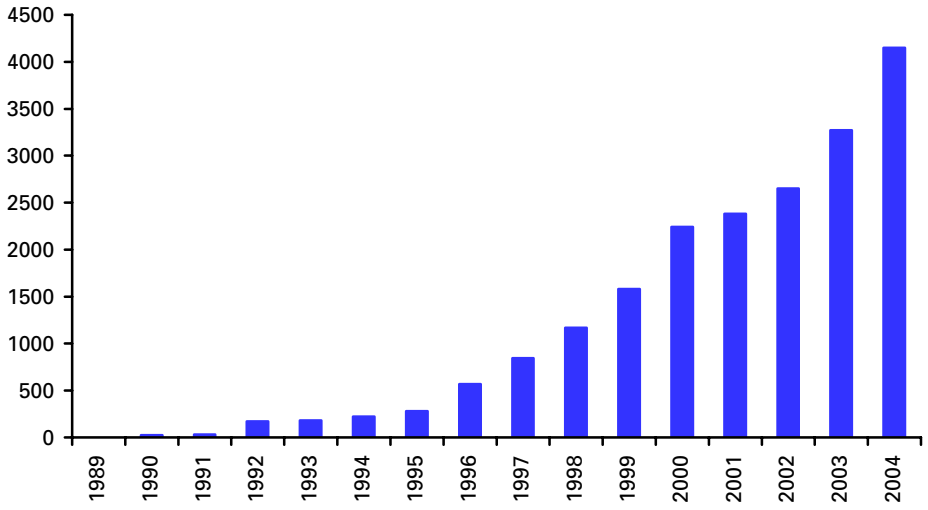
Drug	Indication	Company	Spending ($ m)
Nexium	GERD	AstraZeneca	224
Crestor	Hypercholesterolaemia	AstraZeneca	212
Cialis	Erectile dysfunction	Lilly/ICOS	176
Levitra	Erectile dysfunction	GSK/Bayer	157
Zelnorm	IBD	Novartis	146
Prevacid	GERD	TAP	128
Flonase	Allergy	GSK	122
Singulair	Asthma/Allergy	Merck & Co	122
Lipitor	Hypercholesterolaemia	Pfizer	120
Plavix	Thrombosis	Sanofi-Aventis/BMS	118

Source: Nielsen

Huge extra cash

Since TV advertising in the US was permitted in 1996, industry spending on DTC advertising has witnessed tremendous growth. Over $2.3bn was spent on TV advertising in 2003, with the balance arising mainly from spending in magazines. In 2003, four drug companies spent over $300m on DTC advertising, namely Pfizer, GSK, Merck and AstraZeneca, with Pfizer spending a massive $688m! This growth has been driven, in part, by the change in legislation mentioned earlier, but also because drug companies have found it to be an effective medium for promoting their products, as consumers are placing a greater focus on their health.

Figure 69: DTC spending 1989-2004 ($m)

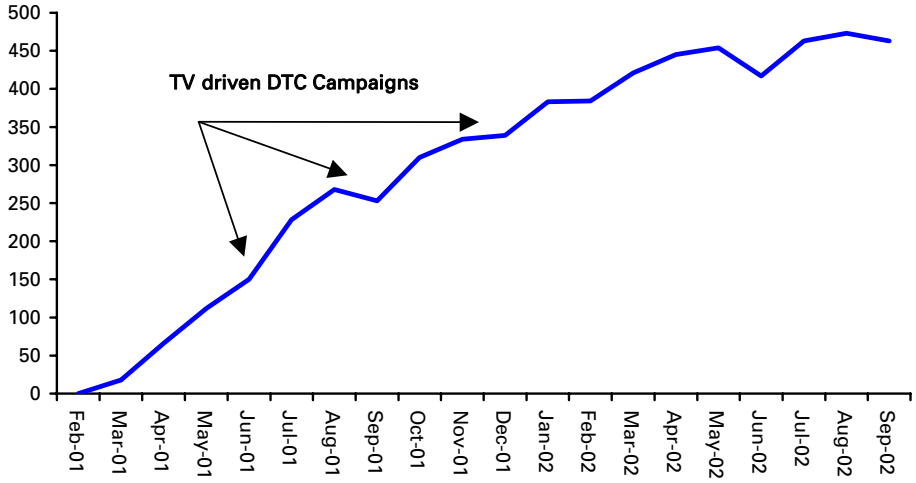


Source: Nielsen

The benefits of DTC advertising can be well illustrated by looking at the sales performance of drugs that have been advertised using this medium. Two features are evident:

- **Market expansion**: DTC campaigns have been able to expand markets for a number of drugs by successfully increasing the number of consumers who are aware of their illnesses and persuading them to go to their doctors and seek treatment with the product advertised. This is well illustrated in the performance of AstraZeneca's *Nexium*, an ulcer/GERD therapy for which sales improved significantly following DTC advertising.

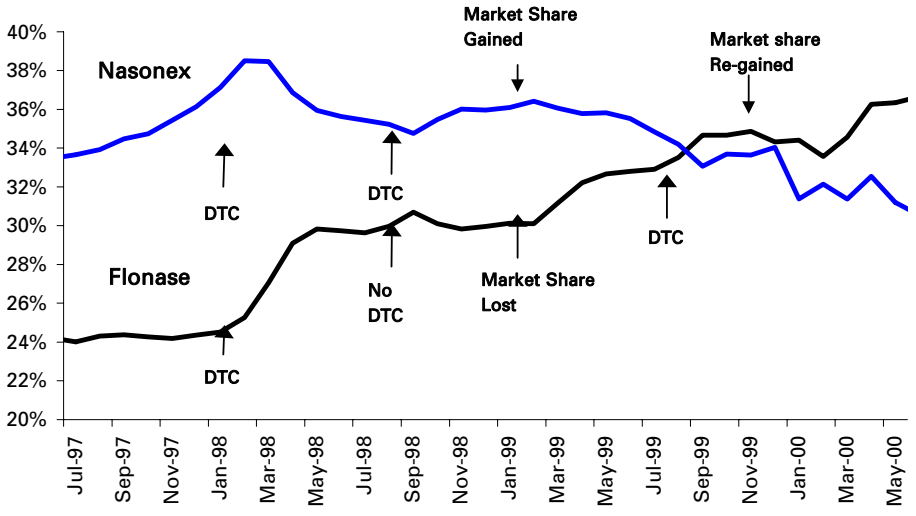
Figure 70: Impact of DTC on US Nexium sales expansion (Rx '000s)



Source: IMS Health

- **Market-share maintenance:** This is most apparent in therapeutic areas, where most of the products are DTC advertised, with manufacturers using advertising to defend or increase market share. As illustrated in the figure below which depicts movements in market share between Schering-Plough's *Nasonex* and Glaxo's *Flonase*, the use of DTC campaigns has become key in influencing prescription trends.

Figure 71: DTC can influence US market shares



Source: IMS Health

DTC advertising has come under recent criticism, however, as consumers have become inundated with pharmaceutical advertisements and politicians have used the massive DTC budgets of the drug industry to balk at the high prices of prescription drugs in the US. This issue has heated up, in particular, following the withdrawal of Merck's Vioxx and increased scrutiny of the COX-2 inhibitor class. In the wake of the Vioxx withdrawal, many politicians and physicians alike agreed that the COX-2 drugs were over-utilised in patients who could have been equally well treated with a cheap, generic NSAID versus an expensive, branded COX-2. This over-utilisation is largely believed to be attributable to the excessive DTC marketing efforts of COX-2 manufacturers Pfizer and Merck who spent $118m and $72m, respectively, on DTC advertising for their leading COX-2s Celebrex and Vioxx.

Although the FDA appears unlikely to re-introduce pre-1997 type restrictions on DTC advertising, at the time of publication, there have been calls for companies to delay the initiation of DTC campaigns until after the drug has been on the market for one or two years and the safety profile is better understood. One company, Bristol-Myers Squibb, has already voluntarily agreed to a one-year DTC moratorium for new drugs post launch. However, it remains to be seen how the rest of the industry will respond and if any legislative efforts to restrict DTC advertising will come into effect.

Analyst considerations when assessing new drug launches

Expanded sales forces and the advent of direct-to-consumer marketing have recently led to the take-off of new drugs following launch. As a result, the success of a new drug is being judged by analysts much earlier than before. However, the launch profile of a drug is likely to vary considerably depending on the disease at which it is targeted.

In a disease for which physician visits are common and where patients are generally given short courses of treatment, we would expect a successful drug to enjoy a rapid take-off. Products in this category would include anti-ulcer drugs and antibiotics.

In contrast, a drug targeted at a disease for which the majority of patients receive long-term therapy would generally experience a slower launch than a drug for acute treatment. This is because a significant proportion of patients receive repeat prescriptions, which a doctor would only normally change in the event of poor control of symptoms or side-effect problems. However, within this category, the level of conservatism varies from disease to disease.

- In conditions where physicians perceive no great risk in changing a patient's therapy, such as high cholesterol, a strong take-off could still be achieved, particularly if a new product is believed to be more effective than existing therapy.
- By contrast, diseases for which drug therapy needs to be finely adjusted and where disruption can lead to serious events (such as epilepsy) tend to see very low levels of switching. As a result, the take-off of new drugs tends to be very slow, driven predominantly by the diagnosis of new patients.
- Of course, the speed of take-off for drugs that are used in chronic therapy also depends on the size of the potential patient population. As a result, drugs to treat common conditions such as high blood pressure can enjoy strong launches, even though the majority of existing patients are on repeat prescriptions.

Drugs that are targeted at diseases that had previously not been routinely treated by primary care practitioners are also likely to experience a slow launch. In these cases, the pharmaceutical company needs to build the market from scratch by educating physicians and by targeting patients through direct-to-consumer advertising. A classic example here is irritable bowel syndrome, where the majority of patients self-medicate. The speed of take-off for a drug in a new disease depends of the frequency and severity of symptoms experienced

by patients and their level of motivation in going to the doctor. Certain diseases where there is a high level of patient motivation, such as obesity and smoking cessation, have in the past seen very strong launches. Sadly, poor willpower has also made these strong starts short-lived.

Finally, new drugs with genuine life-saving potential in a disease where existing therapy is ineffective, such as breakthroughs in cancer treatment, tend to achieve a high level of patient penetration relatively quickly. However, the majority of cancer drugs see their sales build gradually as use expands from second- or even third-line use in a specific tumour type to first-line use in a broader range of cancers.

Patents & market exclusivity

As with any research-based industry, the pharmaceutical industry can only be economically viable if the huge investment required to innovate and develop new medicines results in a benefit to the innovator. For the research-driven manufacturer, this benefit and, indeed, the incentive to continue to invest vast sums of money in research, depend vitally on a company's ability to patent its discoveries. By protecting intellectual property, patents provide research-based companies with a necessary period of market exclusivity to recoup their investment and provide the capital for further innovation.

Following the 1995 GATT accord, patent rights were recognised and harmonised internationally and an international minimum standard for patent term length established. This was agreed at 20 years from the date on which the patent application is filed with the relevant authority, for example, the European Patent Office in Europe, the US Patent and Trademark Office or the Japanese Patent Office. However, for those patents filed before 8 June 1995 the period of patent protection runs for the greater of the 20-year term or 17 years from the issue date. In the US, patent details can be found in the FDA's Orange Book.

Most pharmaceutical companies will file a number of patents on any particular drug as they seek to ensure that their invention or discovery is properly protected from imitation. For a patent to be listed on the Orange Book and therefore fall under the auspices of Hatch Waxman legislation (see later), the innovator company must notify the FDA of its issuance by the PTO within 30 days. While certain patents cannot be listed on the Orange Book (among other things, those surrounding a metabolite, tableting or a manufacturing process), several are key:

- **Composition of matter:** This represents the basic patent on the new chemical entity and its molecular structure. Composition of matter patents afford companies the greatest protection and are least likely to be successfully challenged. Typically, it is following the expiry of this patent that generic manufacturers will seek to launch cheaper imitations.
- **Method of use**: A method of use patent seeks to patent protect the process by which the drug acts in the body and prohibit others from using that process to develop similar drugs. Recent patent disputes suggest that method of use (or mechanism of action) patents are increasingly difficult to uphold.
- **Formulation**: Formulation patents cover the formulation developed by the innovator company to enable the drug to pass into the body, reach the relevant organs and achieve the desired medicinal effect. Several types of formulation patent may be issued through the drug's market life as the drug innovator develops new ways to deliver its products. Formulation changes and patents typically represent a key feature of lifecycle management.

Figure 72: Patent types – rRobustness and filing timelines

Typical pharma patent portfolio	Value	Filing
NCE patents (generics/species)	High	Earlier
Mechanism of action patents		
Method of use patents		
Formulation		
NCE salt/solvate/polymorph		
Process patents		
Gene patents	Low	Later

Source: GSK; Deutsche Bank

Market exclusivity

While initial patent life on a new molecular entity usually runs for 20 years from the date of filing, the period between filing and market launch is invariably a matter of several years. The pre-clinical, clinical and approval periods will all eat significantly into any new molecules' patent life. As such, we estimate that, on average, by the time a new pharmaceutical obtains marketing approval, it will have little more than 11-12 years of patent protection.

However, in certain instances, the clinical and regulatory processes can take so long that, by the time it is approved, a new pharmaceutical will have little, if any, patent life remaining. Such a scenario can hardly be seen to favour the innovator. With this in mind, legislation has been drafted in both the US and Europe that affords drugs periods of market exclusivity on the basis of data presented to the regulatory authorities. Two pieces of legislation are key.

- **1984 Drug Price Competition and Patent Term Restoration Act (The 'Hatch Waxman' Act).** Under this law, a five-year period of data exclusivity for innovator products was instituted. This means that applications for generic copies of drugs cannot be submitted until five years after an innovator product has been approved. This period of exclusivity may run in parallel with a drug's patent life or beyond it. Either way, it ensures that the innovator obtains at least five years of market exclusivity. In fact, this is actually probably nearer six given that abbreviated new drug applications typically take a year to approve and cannot be submitted until the five-year exclusivity period has expired (unless a non-infringement certification has been made, in which case the ANDA may be submitted after four years). In addition, new indications for existing products are entitled to a further three years of exclusivity (albeit doctors would probably prescribe off-label for the additional indication). Note that generic filings can be submitted against three-year exclusivity at any time.
- **The EU Directive relating to medicinal products:** This piece of European legislation creates non-patent related marketing exclusivity for medicinal products in Europe comparable to that of Hatch Waxman, but allows for a maximum period of ten years rather than five. However, data exclusivity beyond the ten-year period will not be granted for either new indications or new formulations.

Patent term extensions

In addition, in the US, under the Hatch Waxman legislation, in certain instances, patent term extensions may be available for the active ingredient in a drug if the date of first marketing of the drug was delayed as a result of the regulatory review. For new human drugs, the regulatory period is defined as one-half of the term starting on the date on which the IND is granted (so permitting the start of clinical trials) and ending on the date on which a request for marketing approval is filed, plus the entire period for which the marketing approval is pending. However, any extension given is limited to no more than five years and must not extend the patent life of the marketed product to over 14 years. A petition for the extension must be made within 60 days of marketing approval.

Hatch Waxman and ANDAs (US only)

As a quid pro quo for patent life extension in the US, the 1984 Hatch Waxman legislation also established the procedure that simplified the approval process for generic drugs. In particular, the 1984 law established the procedure for the Abbreviated New Drug Application (ANDA, see Regulatory section) under which a generic drug could use the safety and efficacy data of the innovator. Provided that the innovator's patent and market exclusivity had expired, the generic manufacturer solely needed to demonstrate that its product was 'bioequivalent' to the innovator drug and certify to the FDA that the original innovator patent had expired, would expire on a particular date, was invalid or would not be infringed. Under Section 505(b)(II) Paragraph (IV) of the Act, it was also obliged to notify the patent holder of its intent to launch, if at the time of launch an Orange Book-listed patent was in force.

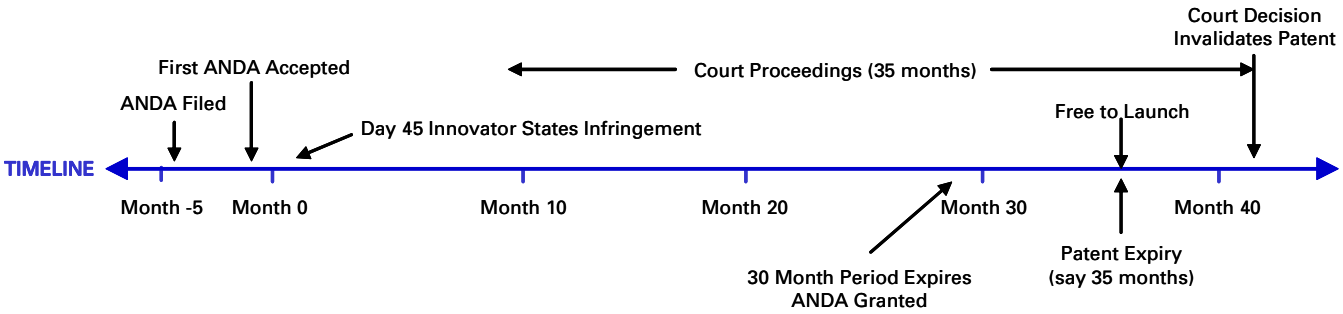
In practice, the workings of the Act are somewhat more complicated than it might at first appear. This is due to two main features: litigation and market exclusivity.

Litigation

Because most innovator companies will seek to extend the patent life of their products and prevent the introduction of generics, they will invariably allege that one of their other many patents is being infringed. Typically, this will be a formulation patent, a polymorph or salt patent, or method of use patent. Having received Paragraph IV notification, the innovator company has 45 days to file a suit alleging patent infringement. Should it fail to do so, no subsequent claim can be made and the FDA will approve the application in the ordinary course of business.

However, assuming the innovator company files for patent infringement, Hatch Waxman prohibits the FDA from granting an ANDA until either the cessation of legal proceedings, which confirm patent invalidity, or 30 months, whichever is earlier. If the generic drug review is completed before either of these points in time is reached, its approval will be deemed tentative, full approval coming once 30 months have passed or a court decision has been reached. Once full approval has been received, the generic company is free to market its generic version once the unchallenged patent or patents (typically substance of matter) have expired. However, it should be noted that it does so in the knowledge that should the court proceedings go against it, it would potentially be liable for damages that are calculated as a multiple of revenue losses suffered by the innovator firm (punitive or treble damages). This process is illustrated by the schematic shown below. (A full overview of the US legal process is provided in the 'US patent litigation' chapter later in this report.)

Figure 73: Timelines associated with Paragraph IV filings



Source: Company data, Deutsche Bank

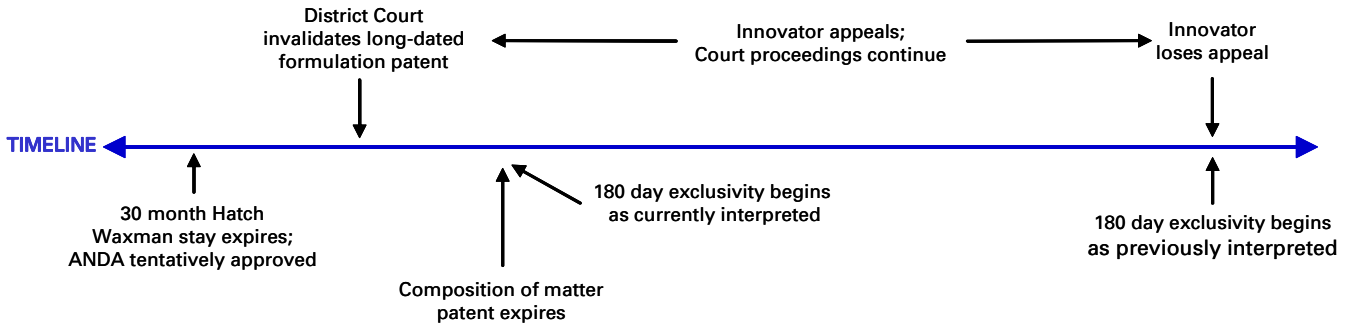
Market exclusivity

In order to encourage the growth of the generics industry and give generic companies an incentive to enter the market at the earliest possible opportunity, the original Hatch Waxman amendments also included provisions permitting 180 days of marketing exclusivity for the generic with first launch entitlement. Given the intense price competition that invariably

follows patent expiration of a large branded drug, this provision was of considerable value to the generic manufacturer, allowing it to garner significant market share at a more favourable price than would be the case were all generics to launch on the market simultaneously. Up until late 2002, the FDA had granted this exclusivity to the first generic to file a complete and acceptable ANDA. However, following the 2002 Prilosec case, the FDA modified the original rules such that market exclusivity is now granted to the first manufacturer to *successfully challenge* the innovator patent, rather than just to the first company to *file* a complete ANDA.

As to when this exclusivity commences, following several court rulings, the FDA announced in early 2000 that it would interpret the phrase 'ruling of the court' used in the 1984 legislation as being the 'ruling of the first court', i.e. the decision from the District (lower) Court. Thus, for Paragraph IV filings made after March 2000, exclusivity now commences from the earlier of first marketing or a ruling of the first court (this assumes, of course, that the ANDA has been approved). This contrasts with the agencies' earlier interpretation that exclusivity would not commence until the earlier of first marketing or the decision of the final or appeal court. Note, however, that the FDA's earlier appeal court interpretation still applies in those cases in which the ANDA application was made prior to March 2002 (i.e. the change is not retrospective). Again, the schematic shown below seeks to reflect both the historic and most recent interpretation.

Figure 74: Paragraph IV filings and 180-day exclusivity


District Court invalidates long-dated formulation patent
Innovator appeals; Court proceedings continue
Innovator loses appeal
TIMELINE
30 month Hatch Waxman stay expires; ANDA tentatively approved
Composition of matter patent expires
180 day exclusivity begins as currently interpreted
180 day exclusivity begins as previously interpreted

Source: Deutsche Bank

Orange Book abuse

One final point. On several occasions in recent years, innovator companies have received and then listed on the Orange Book patents that were issued by the US PTO after an initial Paragraph IV notification had been filed. Having done so, the innovator company would then typically claim that this new patent was also being infringed. Applying its then interpretation of the 1984 Act, the FDA would subsequently enforce a further 30-month period before granting a marketing license to the ANDA filer (assuming no court ruling). Following several high profile cases, not least Bristol-Myers Squibb's antics surrounding BuSpar, GSK's actions on Paxil and Pfizer's on Neurontin, an FTC investigation into the matter led to an FDA pronouncement that from here on, only one 30-month stay would be permissible per ANDA filing.

Paediatric extensions (US only and ex pre-1997 antibiotics)

In order to encourage pharmaceutical companies to undertake studies on drugs that could have meaningful health benefits in children, the Food and Drug Administration Modernisation Act of 1997 (FDAMA) included legislation that afforded companies a six-month exclusivity/patent extension if they submitted data relating to the use of an active drug in a paediatric population. The original legislation expired in 2001, but was immediately renewed. Paediatric studies are defined as at least one clinical investigation in paediatric groups in which a drug is anticipated to be used. The extension is only available in the US and is also only available on those products for which the FDA makes a 'Written Request'. The request

may be issued at the behest of an interested party or on the FDA's own initiative. Trials must be conducted in accordance with the FDA's guidelines, but, assuming that the data submitted meet with the FDA's request, an additional six months of product exclusivity will be granted. Each 'Written Request' may result in only one period of paediatric exclusivity. Note that antibiotics that were the subject of a marketing application received before 21 November 1997 are not eligible for paediatric exclusivity unless they meet orphan drug requirements.

At present, there is no additional period of exclusivity available for paediatric studies in Europe. This is, however, a current area of debate, with the EU considering whether such an incentive should be introduced and if so, what period of exclusivity should be offered (at the time of print the consideration is for an extra six months).

Orphan drugs

In order to encourage research into rare diseases with limited incidence in the population as a whole, legislation in the US, Europe and Japan has been passed for drugs that can be used to treat these diseases. By offering market exclusivity and various tax breaks, health authorities have sought to encourage the industry to undertake research into disease areas that, because of their limited incidence and revenue prospects, generally hold limited commercial appeal.

The first territory to adopt orphan dug legislation was the US, which in 1983 enacted the Orphan Drug Act. This legislation has subsequently served as a prototype for a programme adopted in Japan in 1993 and, most recently, the European Commission (in 2000).

In the US, an orphan disease is defined as either one which affects under 200,000 patients or one which would not recoup development costs on the basis of US sales. Overall, 10-20 million Americans suffer from around 5,000 or so orphan diseases for which there are no available cures, such as multiple sclerosis, narcolepsy, and many genetic disorders. To help these patients, the law provides two principal incentives to try to make it commercially feasible to develop orphan drugs - a seven-year period of market exclusivity post-approval (compared to the normal five years) and a 50% tax credit for certain clinical research expenses incurred in development. In addition, orphan drugs will often attain fast-track approval. Overall, in the US, the approach seems to have worked well, with over 190 orphan drugs approved since its enactment compared to only ten in the decade before.

In Europe, an orphan disease is defined as one that has an incidence of less than five in 10,000. Companies developing such drugs are exempt from some or all of the licensing fees and will be granted exclusivity for up to ten years.

Figure 75: Summary of key FDA exclusivity types

Code	Definition	How long	Examples
NC	New combination	3 years*	Symbyax (Prozac + Zyprexa), Caduet (Norvasc + Lipitor)
NCE	New chemical entity	5 years	Iressa, Levitra, Eloxatin
NDF	New dosage form	3 years*	Zomig ZMT
NE	New ester or salt of active ingredient	5 years*	Valcyte (new ester of Cytovene), Lexiva (pro-drug of Agenerase)
NP	New product	3 years*	Nexium (single isomer of Prilosec)
ODE	Orphan drug exclusivity	7 years	Copaxone (multiple sclerosis), Gleevec (gastrointestinal stromal tumours)
PED	Paediatric exclusivity	6 months	Cipro, Nexium, Epivir

Source: Deutsche Bank estimates and company data
**Only granted if new product approval is based on results of new clinical investigations, not including bioavailability studies.*

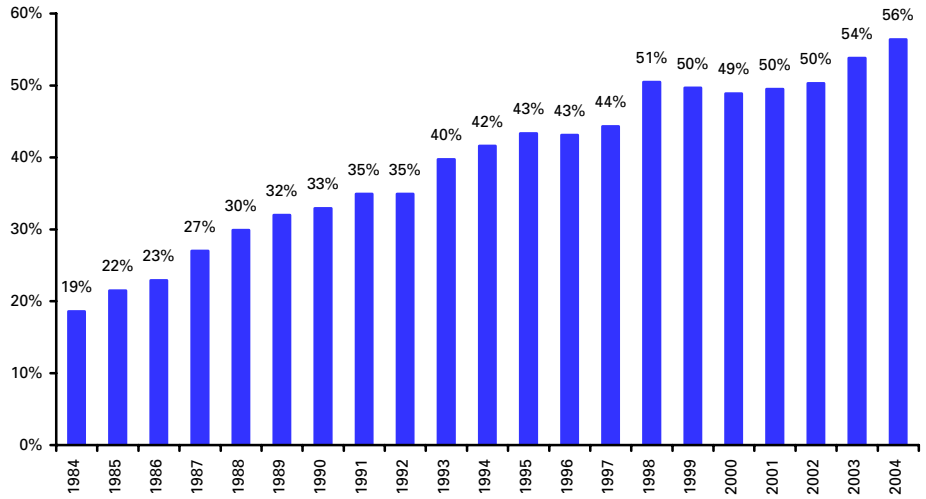
Generic drugs

Once the patent or period of exclusivity expires on a branded product, it is likely to find itself subject to competition from generic versions of the active molecule, most particularly if the branded product was achieving significant sales (in excess of $100m per annum). A generic drug is one that has demonstrated itself to be the 'bioequivalent' of the patented product, i.e. it has the same pharmacokinetics and availability in the body. Because a generic's attributes are the same as the branded or innovator drug (in effect, it is exactly the same molecule), its only true form of differentiation from the innovator brand is price.

Hatch Waxman established today's generic industry

The modern generics industry in the US was firmly established following the 1984 Hatch Waxman Act. In return for allowing innovator products greater market exclusivity, the Act allowed the generic manufacturer to use the product innovator's drug safety, efficacy and toxicology data when filing for FDA approval. This greatly reduced the cost of generic applications and the time taken to gain approval. In essence, all the generic manufacturer needed to demonstrate was that its version of the already approved innovator product was bioequivalent.

Figure 76: Generic drug share of US prescription markets 1984-2004



Source: IMS Health

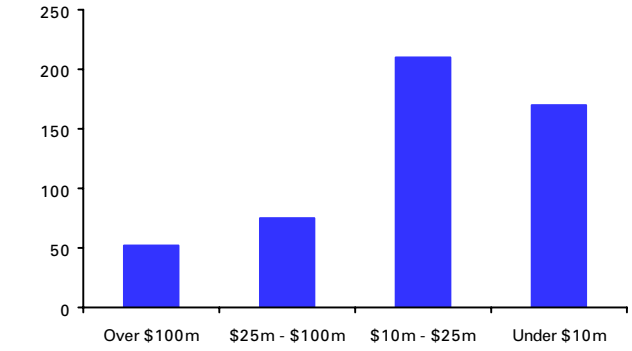
Generics account for over 50% of US drug market

The consequence of the Act has been strong growth of the US generic market. As demonstrated by the figure above, in 2004, generics accounted for over 56% of the prescription drugs market by volume, compared to 19% in the year the law was first enacted (1984). With several large products facing patent expiry over the next few years, we expect generic prescriptions will continue to show further market share gains.

In general, once the patent/exclusivity period for a branded product expires, generic competition will commence almost immediately. As more and more generics enter the market, price erosion will intensify. Depending upon the number of entrants, it is not unusual to see generic prices in the US market at only 20-25% of that of the patented product. Today, as illustrated by the generic erosion chart for BMS' Glucophage, the influence of managed care and modern technology on buying patterns has shown that most large products facing

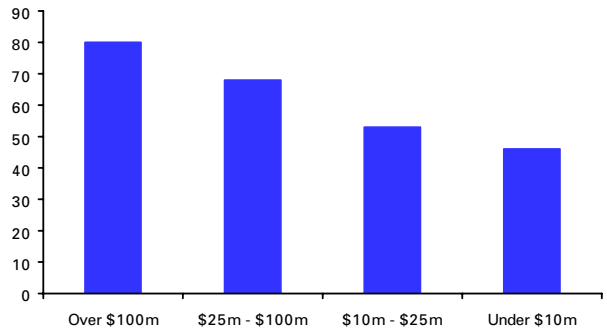
patent expiry can expect to lose between 70% and 80% of their monthly US revenues within two months of expiry. This contrasts with a more typical 70-80% over 12 months seen in the late 1990s and bears testament to the efficiency of the US system.

Figure 77: Days to first generic entrant



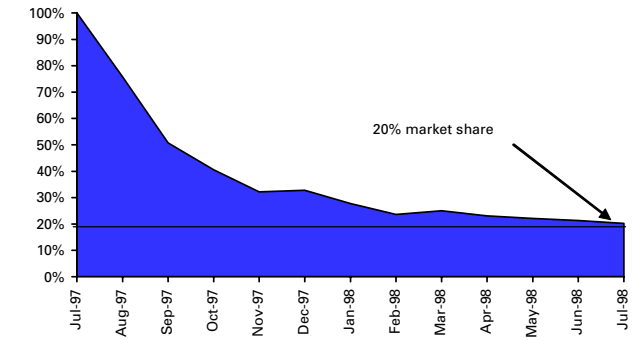
Source: Health Services Research

Figure 78: Percentage with generic competition



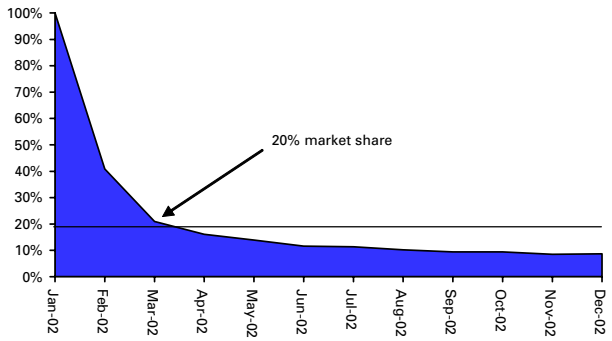
Source: Health Services Research

Figure 79: Zantac patent expiry (% sales lost, 1997)



Source: IMS

Figure 80: Glucophage patent expiry (% sales lost, 2002)



Source: IMS

Generic erosion is fastest in the United States

The extent of generic erosion varies in different geographic markets depending on both legislation and physicians' attitudes towards costs. Erosion of branded drugs tends to be the most rapid in the US, driven by the profit opportunity and the desire of private managed care organisations to keep costs down (note that US branded prices are about 30-40% higher than elsewhere in the world, whereas US generic are typically priced at 75-80% less than the brand). One might have expected that where government bodies are the central purchasers, i.e. in Europe and in Japan, generics would also hold a large share of end-markets and that conversion from a branded drug to a generic would be rapid. This, however, is generally not the case and of the larger markets, it is only really in the UK and Germany that generic erosion occurs at a significant pace. The key difference between the US and Europe in this regard is the practice of generic substitution by the pharmacist. This means that in the US, it is legal for the pharmacist to dispense a generic equivalent of a drug that the doctor has prescribed by brand. This is illegal in most European countries. Generic penetration is high in Germany and the UK, because doctors in both of these countries have incentives to be cost conscious and as a result, tend to prescribe drugs using their generic names.

In addition, it is worth noting that the differential between branded and generic prices is much greater in the US as compared to many other countries and thus the cost savings to be

achieved by the insurer or government are much greater. In contrast, in many European countries, for example, generics are often priced at only a modest discount to the branded price. This price differential is illustrated by Figure 81which depicts generic volume and value shares in key global markets. In the US, the value of share of generics is only one-third of the volume share, whereas in several European markets the value share is 50-70% of the volume share.

Having said this, the pressure on government health budgets across Europe has meant that governments are now actively seeking to promote generic markets as a means of containing the growth in prescription drug spending. Thus, in France, 2002 has seen the government reach agreement with physicians, encouraging them to write prescriptions using the international non-proprietary (INN or generic) name rather than the brand. Likewise, in several Scandinavian countries, consideration is now being given to permitting generic substitution where it was not previously allowed.

Figure 81: Generic market share in different geographic areas (2004)

---------- Large generic markets ----------			---------- Limited generic markets ----------		
	% Generics			% Generics	
Country	**by volume**	**by value**	**Country**	**by volume**	**by value**
US	56	17	Spain	7	5
Germany	41	23	Japan	16	5
UK	55	24	Italy	4	2
			France	10	7

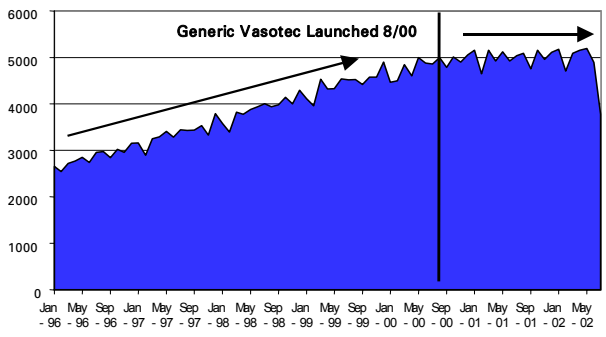
Source: IMS, European Generic Medicines Association

Therapeutic substitution

The next five years are likely to see a significant number of innovator products facing generic competition as their patents expire. Shown overleaf, our estimates suggest that in the four years between 2005 and 2008, products with US revenues alone of over $40bn will face generic competition for the first time. In several cases, entire classes of drugs look likely to see a substantial loss of sales as key products lose protection, not least the cholesterol-lowering statins and the anti-depressants.

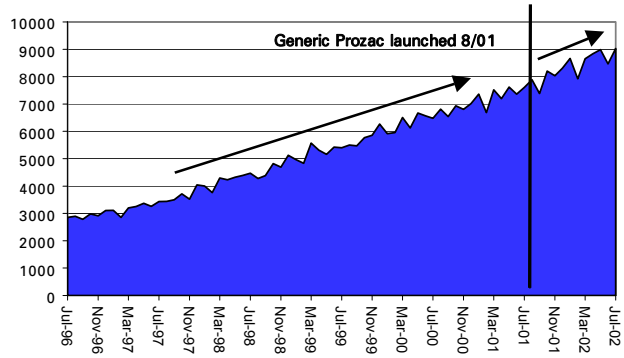
As discussed earlier, historically, the advent of generic competition following the loss of patent protection on any one brand has resulted in significant generic substitution. This loss has not, however, resulted in a meaningful deterioration in the growth of other therapies in the class, as US payers have proved reluctant to actively encourage the substitution of a patented, branded drug in the same therapeutic class with a cheaper generic, i.e. enforce therapeutic substitution.

Figure 82: Post-Vasotec market growth stalls (branded TRx per month ex Vasotec)



Source: IMS Health; (ex Altace)

Figure 83: Post-Prozac market growth continues (branded TRx per month ex Prozac)



Source: IMS Health

Figure 84: Key US patent expiries 2005-2008 (Sales are 2004 US sales)

Brand	Generic	Company	US Sales	Expiry	Brand	Generic	Company	US Sales	Expiry
2005					**2006**				
Flonase	fluticasone	GSK	US$824m	May-04[1]	Allegra	fexofenadine	Sanofi-Aventis	US$1,484m	expired[2]
Duragesic	fentanyl	J&J	US$1,266m	Jan-05	Trileptal	oxcarbazepine	Novartis	US$391m	Jan-05[3]
Biaxin	clarithromycin	Abbott	US$458m	May-05	Adderall XR	amphetamine	Shire	US$596m	expired[2]
Rocephin	ceftriaxone	Roche	US$642m	Jul-05	Pravachol	pravastatin	BMS	US$1,420m	Apr-06
Zoladex	goserelin	AstraZeneca	US$152m	Aug-05	Proscar	finasteride	Merck	US$368m	Jun-06
Amaryl	glimepiride	Sanofi-Aventis	US$268m	Oct-05	Zocor	simvastatin	Merck	US$3,613m	Jun-06
Zithromax	azithromycin	Pfizer	US$1,393m	Nov-05	Zoloft	sertraline	Pfizer	US$2,657m	Jun-06
Cefzil	cefprozil	BMS	US$161m	Dec-05	Ambien	zolpidem	Sanofi-Aventis	US$1,486m	Oct-06
					Zofran	ondansetron	GSK	US$1,034m	Dec-06
					Lamisil	terbinafine	Novartis	US$528m	Dec-06
2007					**2008**				
Lotrel	amlodipine + benazepril	Novartis	US$920m	Jan-07[2]	Depakote	divalproate	Abbott	US$978m	Jan-08
Norvasc	amlodipine	Pfizer	US$1,991m	Jan-07	Camptosar	irinotecan	Pfizer	US$449m	Feb-08
Zosyn	piperacillin + tazobactam	Wyeth	US$395m	Feb-07	Fosamax	alendronate	Merck	US$1,771m	Feb-08
Videx	didanosine	BMS	US$106m	Mar-07	Serevent	salmeterol	GSK	US$639m	Feb-08
Coreg	carvedilol	GSK	US$778m	Mar-07	Trusopt	dorzolamide	Merck	US$236m	Apr-08
Clarinex	desloratidine	Schering-Plough	US$420m	Jun-07	Requip	ropinirole	GSK	US$97m	May-08
Imitrex	sumatriptan	GSK	US$900m	Jun-07[2]	Sonata	zaleplon	King	US$73m	Jun-08
Tegretol XR	carbamazepine	Novartis	US$103m	Jul-07	Effexor XR	venlafaxine	Wyeth	US$2,264m	Jun-08
Toprol	metoprolol	AstraZeneca	US$977m	Sep-07	Lamictal	lamotrigine	GSK	US$758m	Jul-08
Zyrtec	cetirizine	Pfizer/UCB	US$1,287m	Dec-07	Casodex	bicalutamide	AstraZeneca	US$232m	Oct-08
Tequin	gatifloxacin	BMS	US$124m	Dec-07	Altace	ramipril	Wyeth/King	US$390m	Oct-08
Kytril	granisetron	Roche	US$150m	Dec-07	Zerit	stavudine	BMS	US$119m	Dec-08
Risperdal	risperidone	J&J	US$1,711m	Dec-07	Prevacid	lansoprazole	TAP	US$2,592m	Sep-08

Source: Deutsche Bank, FDA Orange Book Note we do not assume paediatric extensions or supplementary protection unless granted.
(1)Generics delayed pending issuance of FDA guidance for intranasal generics. (2) Assumes loss of litigation regarding later dated patent. (3) No patents listed. Assumes generics 12-15 months post expiry of NCE exclusivity

Whether this remains the case has yet to be seen. However, as the benefits of one drug over another in the same therapeutic class become more marginal and cost becomes a more significant issue, the case for driving therapeutic substitution in the US market will become stronger. Indeed, looking at recent expiries, it does now seem that in classes where products are poorly differentiated, the advent of generic competition against the category leader does result in a moderation in the growth profile of the entire class. This is illustrated by the impact of the heart drug Vasotec's expiration (the class leader) on growth in the branded ACE inhibitor class. By contrast, as the accompanying analysis of the anti-depressant class after Prozac's expiry shows, in a branded class where the drugs are well differentiated, little if any difference in the growth profile is discernible.

Patent life-extension strategies

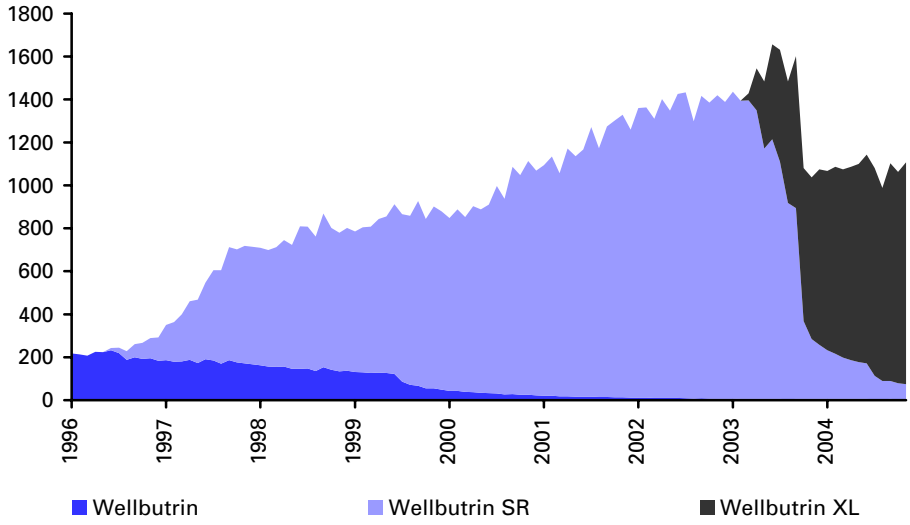
The threat of a large impending patent expiry for any leading research-based company should not be underestimated. After all, looming patent expiries have been largely responsible for much of the merger and acquisition activity witnessed over the past decade. Indeed, for any $1bn product, every day that generic entry is deferred is worth at least $2.7m to revenues and probably well over $2m to gross profits. This is quite an incentive to defer the inevitable day of reckoning.

Thus, not surprisingly, the leading ethical pharmaceutical companies have developed several strategies to extend the life of their products and with some degree of success. Discussed

below, these vary from the now almost inevitable litigation to altered formulations and isomers of existing drugs.

- **Litigation**: Almost all pharmaceutical companies will have in place a host of patents surrounding any one drug. Beyond composition of matter patents, these invariably include patents surrounding the active molecule's formulation, its mechanism of action and its manufacture. The slightest whiff of a generic threat and litigation is almost bound to follow, some form of patent infringement being cited. And if the first court ruling goes against the innovator, there is always the chance to appeal. Of itself, litigation typically buys the innovator several months of extra time, not least because such litigation almost invariably runs well past the patent expiry date. Increasingly, we are, however, seeing the courts rule in the generics' favour.

Figure 85: Wellbutrin franchise retention via line extensions (TRX)



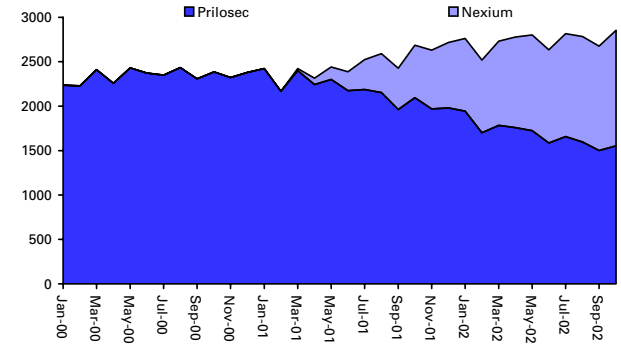
Source: IMS

- **Formulations**: A more innovative approach to life extension is to develop an alternative formulation of an existing drug late in its life cycle that offers patients and physicians a definite benefit, yet poses a further challenge to the generic manufacturer. For example, moving from a three times a day formulation to once a day offers compliance benefits for patients, which will be recognised by physicians and yet probably presents an additional challenge to the generic (i.e. developing its own formulation for slow release). Of course, if the generic house is able to develop its own formulation, then the life extension strategy will falter. However, strong formulation competence falls outside the capability of many generic houses. Thus, the more sophisticated the formulation, the greater the protection. As an example, AstraZeneca successfully defended its Prilosec formulation patents against three out of four generic companies involved in the first round of patent litigation, thereby significantly limiting the initial rate of generic erosion. Elsewhere, GlaxoSmithKline's Wellbutrin franchise represents a good example of the use of new formulations to keep generics from capturing market share. GSK's origianl formulation of Wellbutrin, introduced in 1985 required administration three times daily. The company subsequently introduced a twice-daily version, Wellbutrin SR, in 1996 and most recently a once-daily version, Wellbutrin XL, in 2003. As evident from Figure 85, this strategy enabled GSK to retain a significant portion of sales even post patent expiry.

- **Isomers**: Many molecules have two distinct forms – one right handed and one left handed. Although the molecule is identical in its formula and composition, much like a pair of human hands, each isomer (or hand) is a mirror image of the other. Indeed, the pharmacological effect of the molecule often rests with just one of the two chiral forms.

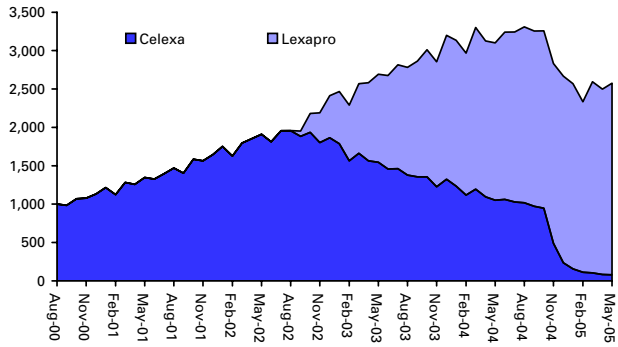
  Several companies have thus seized upon this difference as an opportunity to develop and patent the more pharmacologically active chiral form and market it as a new drug. For example, AstraZeneca's Nexium is a chirally pure form of its anti-ulcer drug Prilosec, as is Schering-Plough's Clarinex follow-up to its leading anti-histamine, Claritin, and Forest/Lundbeck's Lexapro follow-up to its antidepressant Celexa. As 'new' molecules, these pure chiral forms (also called 'enantiomers') are patent protected and often more efficacious or better tolerated than the original drug.

Figure 86: Isomers as a means of protecting franchises – NRx Nexium and Prilosec



Source: IMS

Figure 87: Isomers as a means of protecting franchises – TRx Celexa and Lexapro



Source: IMS

- **Combinations**: Another effective means of extending the life of a successful drug is to develop a combination product and so create a formulation that offers compliance, if not efficacy, benefits, i.e. the patient need only take one drug once a day instead of two, etc. A good example of a combination product is GlaxoSmithKline's HIV drug Trizivir. By incorporating three active products into one pill, Trizivir offers major compliance benefits (one tablet twice a day instead of three tablets twice a day). Moreover, Trizivir and GSK's Combivir, which combines two key HIV agents, have effectively cannibalised the majority of single-agent Retrovir sales (a constituent of both combination drugs), which is expected to see generics in 2005.

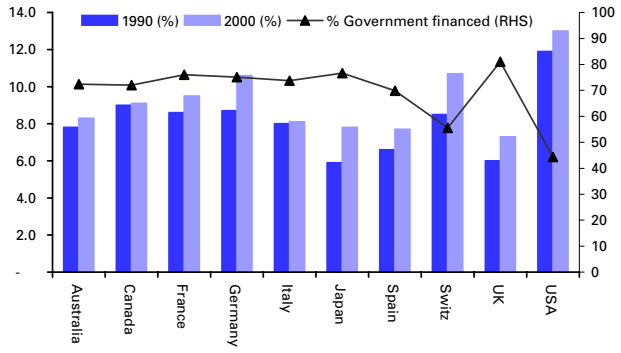
Funding and pricing of pharmaceuticals

The provision of an adequate system of healthcare is seen as a basic right of the citizen in almost every economy – developed or not. Indeed, access to affordable healthcare for all citizens is one of the primary objectives of any developed economy. As such, healthcare is a major political issue for governments across the world, as is its cost. For any nation, funding the provision of basic health services represents a significant percentage of gross domestic product (GDP), as illustrated in Figure 88. What's more, as we live longer and the cost of providing medical treatment such as hospitalisation, medicines, surgery and nursing continues to rise, the provision of an acceptable level of healthcare for the population is becoming an ever larger burden on the government's purse.

Given the choice, we suspect that most governments would more actively promote private funding of healthcare and reduce the funding burden that the provision of a national system of healthcare represents. However, this is of course politically unacceptable in most, if not all, democratic nations. As such, within the major industrialised nations, it is only in the United States that government still plays a minority role in the purchase and provision of healthcare for its citizens. Equally, it is only in the US where a free market for the pricing of drugs exists. Of course, private medicine is available in most other countries. However, outside the US, government authorities typically determine price and provision with every effort being made to hold cost down. Thus, pharmaceutical prices are determined by the State with an effort made to contain prices and usage wherever possible. This probably does little to help contain overall costs. Prescription drug therapy is highly cost effective and often circumvents the need for other more expensive interventions such as surgery, hospitalisation, physician visits and nursing care. Nonetheless, of themselves, prescription drugs represent an important component of healthcare costs and, being provided by highly profitable and private organisations, are an easy political target for governments trying to contain cost.

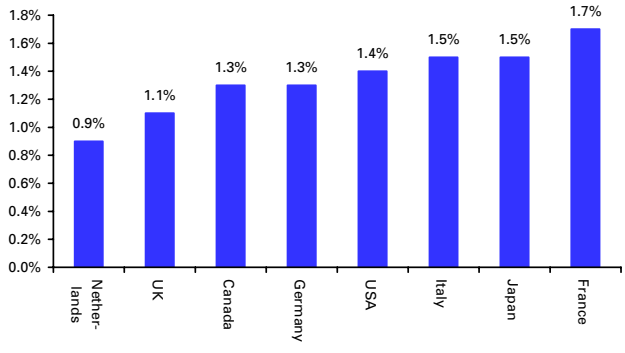
The variety in national models for the provision of healthcare means that almost every system has its differences. Starting with the US, the world's most significant economy and the pharmaceutical industry's most important, over the next few pages, we summarise the provision of healthcare in the major economies of the developed world.

Figure 88: Healthcare as a % GDP (1990 and 2000)



Source: OECD HealthData

Figure 89: Pharmaceutical costs as % GDP (1997)



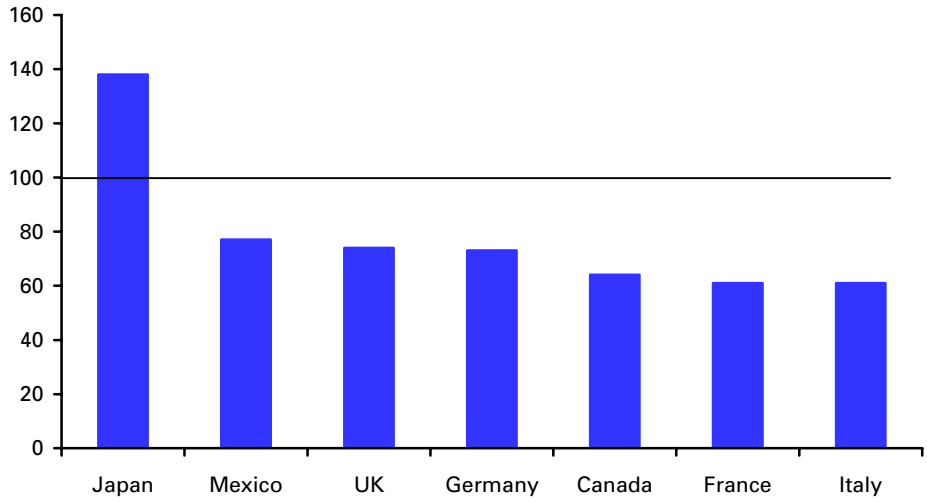
Source: OECD HealthData

United States

The US currently devotes a higher percentage of its GDP to health expenditure than any other industrialised nation, a gap that has widened over the past 20 years. In 2000, total national health expenditure in the US amounted to roughly $1.2trn, or 13.2% of GDP. Importantly, the share of GDP allocated to health has nearly doubled since 1970, when it was just 6.9%. With the elderly population forecast to rise to 20% of US citizens by 2020 from 12.5% today, healthcare expenditures can only be expected to rise further as a proportion of GDP, placing considerable pressure on healthcare financing and society in general.

The significance of healthcare costs has also led to increasing calls for greater regulation of pharmaceutical pricing. As things stand, the US remains the only significant market in which manufacturers can set the price of drugs without any government-imposed limitation. In addition, the import of drugs has been illegal, preventing wholesalers and users from taking advantage of drug prices that can be substantially cheaper outside the US. As European and Japanese authorities continue to target the cost of medicines as a means of controlling healthcare expenditures, the difference in prices between the various regions in the near term can only continue to expand.

Figure 90: Prices by territory as a percentage of US prices (1999)



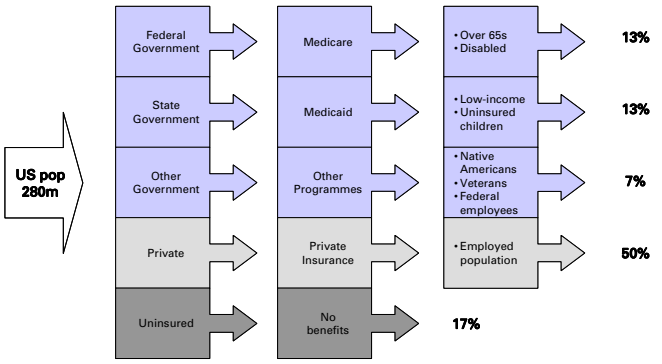
Source: Danzon and Furukawa, Health Affairs, October 2003

Given the discrepancy in prices between the US and elsewhere in the world, it is perhaps surprising that while healthcare expenditure as a proportion of GDP runs well ahead of other industrialised nations, expenditure on pharmaceuticals is in line with that of other nations. We suspect that in part, this apparent anomaly reflects the historical absence of a state-funded prescription drug benefit for the majority of those over the age of 65 and the consequent under-utilisation of prescription drugs as a form of preventative medicine for much of the elderly population. (Note this is all about to change from January 2006 with the introduction of the Medicare prescription drug benefit which is discussed later in this section.)

Managed care has seen explosive growth

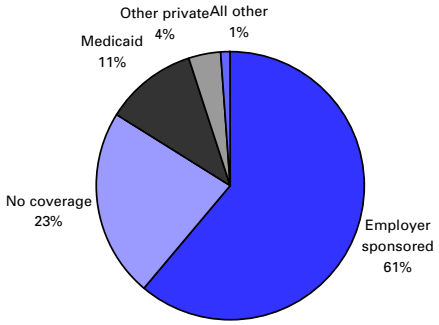
The way that healthcare is delivered and paid for in the US has been undergoing rapid, market-driven changes in recent years. Most significantly, the provision of healthcare insurance has become an expected component of most employees' remuneration package. At the same time, in an effort to contain associated costs, employers have increasingly outsourced the management of that benefit to specialised managed care organisations.

Figure 91: Coverage by type (% 2000)



Source: IMS Health

Figure 92: Non-elderly drug coverage 2004



Source: Kaiser Family Foundation

Over 90% of employed Americans are now covered by some form of managed care organisation, compared to less than 10%, 20 years ago. These managed care organisations use their enhanced buying power to demand cost reductions from the providers of drug and healthcare services and are today responsible for administering the healthcare needs for over half the US population. In stark contrast to almost every other industrialised nation, the government is a minority provider. Overall, the US government funds the healthcare costs of under a third of the US population.

Managed care programmes

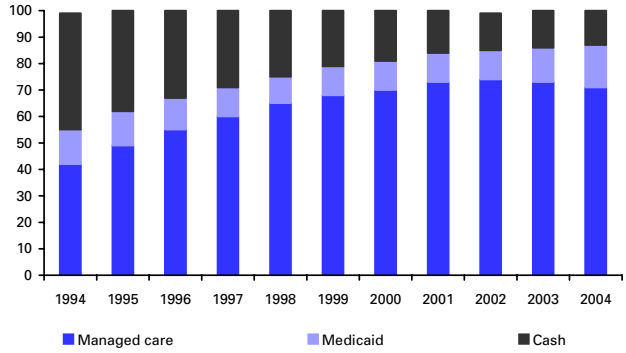
As stated, around 90% of employed Americans now receive their healthcare benefits through a managed care organisation. These managed care programmes have aggressively leveraged their greater buying power to negotiate sizeable discounts from the drug manufacturers – typically of the order of 20% or so. Over the past several years, a multitude of different plans providing varying levels of flexibility and benefit have been established. These include health maintenance organisations (HMO), preferred provider organisations (PPO) and point of service plans (POS). The essential features of each are highlighted below.

Healthcare maintenance organisations (HMO)

There are three types of HMO in existence. In order of increasing flexibility, these are:

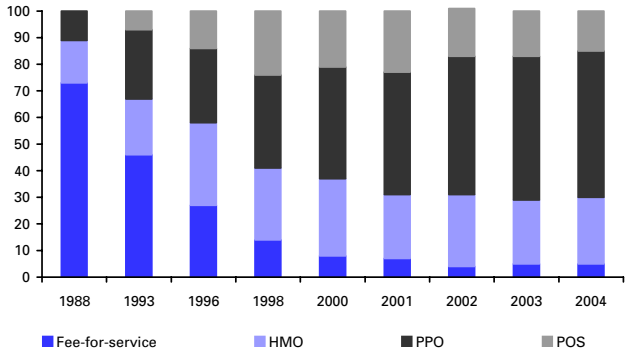
- **Staff model HMOs**: In this model, individuals see a doctor employed by the HMO, who may prescribe drugs from an approved list (i.e. a formulary) set by their HMO.
- **Group model HMOs:** Here, the doctor is self-employed and is contracted to work for one HMO. Again, less choice is available to the patient, as their doctor must work from a formulary. Prescribing patterns are closely monitored and should the physician fail to adhere to formulary requirements, he risks losing his HMO contract.
- **Network HMOs and independent physician associations (IPAs)**: Within this type of organisation, doctors are under contract to a number of different HMOs, each of which typically runs its own formulary. It is invariably difficult for the physician to remember which drug may be prescribed under a specific plan. As such, they often prescribe the treatment that they consider most appropriate.

Figure 93: Drug reimbursement by managed care



Source: IMS

Figure 94: Employer-sponsored health coverage



Source: Kaiser Family Foundation

Point of service (PoS): Under point of service plans, individuals can visit a selection of doctors specified by their insurer/plan manager. The elected doctor is then responsible for providing patients with their basic healthcare, referring them to specialists should the need arise. Patients wishing to take up the services of a specialist will often pay an additional out-of-pocket fee.

Preferred provider organisations (PPO): Alternatively, patients can also chose to consult a number of doctors recommended by their plan manager. The doctors will then discount the cost of their services to be reimbursed by the managed care organisations in return for volume of patients referred to them. Patients can also consult a doctor who is not on the list, but will be subject to a higher out-of-pocket cost.

Fee for service indemnity: This is by far the most flexible of all health insurance plans and was the most common structure prior to the take-off of managed care. Under the 'fee for service' programme, individuals simply choose which doctor they wish to see and receive the treatment considered most relevant for their condition by the doctor. Rising premiums associated with the flexibility offered have, however, seen patients switching to the aforementioned PPO and PoS programmes, which, while less flexible, are far more affordable.

Pharmacy Benefit Managers (PBMs)

Although managed care now looks after the healthcare needs of around half of the US population, the industry itself remains very fragmented, with over 1,600 managed care organisations of one type or another operating in the US market today. However, by outsourcing the management of the pharmaceutical needs of their members to organisations called pharmacy benefit managers (PBMs), managed care has achieved greater mass and buyer leverage in prescription drug markets. In effect, the PBMs are organisations that administer the prescription drug benefits on behalf of insurers, HMOs and other drug sponsors. By aggregating purchasing and administration for plan members, they are able to save significant costs for their customers, the HMOs, not least through negotiating discounts on drugs with the pharmaceutical manufacturers themselves.

Over the past five years, the PBM industry has seen considerable consolidation. As such, the top three companies in the industry now process around 40% of all US prescriptions. Given that they design a significant proportion of HMO drug benefit plans, this provides them with substantial negotiating clout. More often than not, if large cap pharma is to have a new drug listed on a HMO formulary, it will need to reach agreement on price, etc, with the PBM that manages that formulary's needs. In an age when many 'me-too' and generic products are coming to the market, this is placing increasing pressure on drug prices.

Figure 95: Leading three PBMs manage 40% of US market

	Caremark	Medco	Express Scripts	National total	PBM share
Enrolled lives[1]	97m	67m	57m	296m	
Annual drug spend	$30bn	$35bn	$15bn	$235bn	34%
Rx claims processed					
Retail	555m	415m	399m		
Mail order	47m	88m	39m		
Adjusted total[2]	696m	678m	516m	3950m	48%

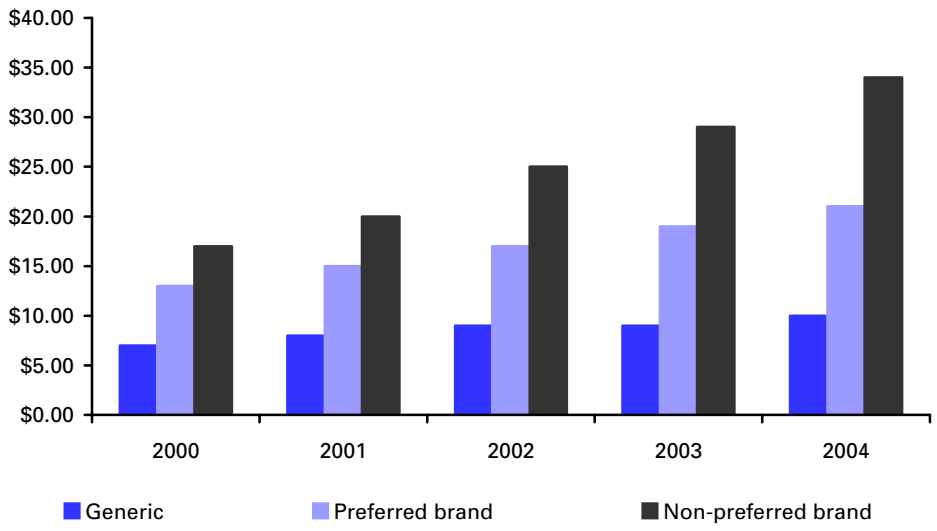
Source: Deutsche Bank
(1) PBM total is disproportionate to national total due to double counting of members. (2) Each mail order prescription counts as three retail prescriptions.

Co-payments and cost-reduction initiatives

For several years, managed care companies have been trying to contain drug costs by initiating tiered co-payment schemes. These are basically schemes whereby the consumer of the drug has to pay a differential co-payment on medicines obtained, depending on the status of the drug within the managed care organisation's formulary. From the insurer's perspective, such an approach provides it with some leverage over consumer preference, so saving it money. However, as managed care's ability to influence the consumer decision grows, so too does its negotiating position with the pharmaceutical manufacturer. Initially, the managed care organisations launched two-tier programmes. Three-tier programmes have, however, quickly followed these. In some instances, an even greater number of tiers are now being built into plans.

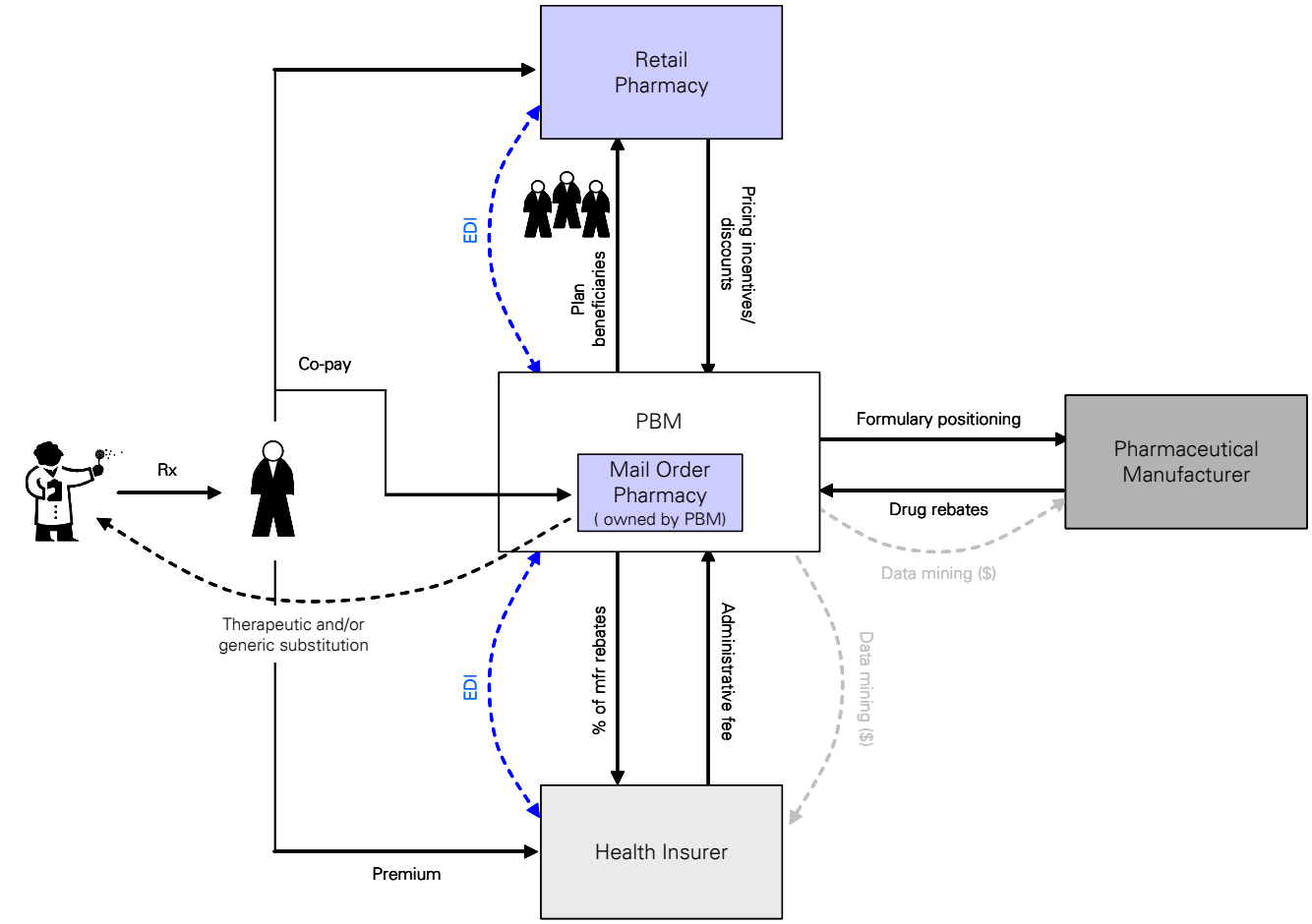
The concept of co-payments is a simple one: the patient can have the medicine he or she wants, but depending on the tier, the patient will be required to pay a greater or lesser contribution to the cost of the drug. In most multi-tier prescription drug programmes, generic drugs usually comprise the lowest tier. The second tier is for preferred drugs, where the co-payment is slightly higher. The third tier is usually reserved for non-formulary drugs and features the highest co-payment, in the range of $25–$50. Beyond keeping costs down, the key feature is to try and inject some price awareness and, subsequently, price elasticity into the pharmaceutical market.

Figure 96: Co-payment tiers are rising



Source: Deutsche Bank

Figure 97: Map of the US pharmaceutical industry



Source: Deutsche Bank EDI = electronic data interface

Publicly funded health insurance programmes

A number of federally funded programmes exist nationwide. Most significant among these are Medicaid for those on low incomes and Medicare for the elderly and disabled.

Medicaid

Medicaid is funded jointly by the state and federal governments and pays for cost of hospitalisation, visits to doctors and prescription drugs for those with low incomes. It covers an estimated 44 million Americans and in 2002, Medicaid expensed an estimated $28bn for prescription drugs. For the pharmaceutical companies, there is, however, an incremental cost of Medicaid business. In 1990, Congress required that, in order to have a drug reimbursed by the Medicaid programme, the drug manufacturer would have to pay a rebate on the product supplied.

For all innovator products, reimbursement requires a rebate that is the greater of 15.1% of the average manufacturer price (AMP) or the difference between the list price and the manufacturer's 'best price' (typically the discount offered to private managed care bodies). In addition, a further rebate is demanded for any price increase that exceeds the rate of consumer price inflation. Reimbursement for generic drugs requires a rebate of 11% of each manufacturer's AMP. In 1999, manufacturers returned an estimated $3.3bn to the federal and state bodies.

In addition to requiring rebates, as state budgets have become tighter, so many state Medicaid programmes now run restrictive drug formularies, as well as limiting the number of

prescriptions for any one patient that may be reimbursed. Following the success of the states of Florida and Michigan in implementing formularies, which, for non-approved products, require prior authorisation for reimbursement, several other US states are also looking at the use of restricted lists to contain expenditure on expensive new medicines. The provision of Medicaid benefits has also been increasingly outsourced to the managed care groups as a means of controlling costs. Over 50% of Medicaid recipients are now enrolled in some type of managed care, of which there are three basic types. For reference, these are:

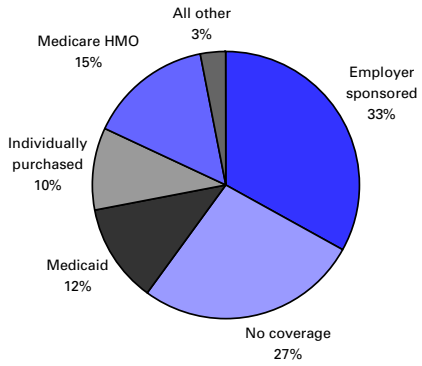
- Full-risk capitation, in which states contract with the managed care provider and pay a fixed fee per enrollee per month to outsource full-risk health insurance coverage.
- Partial capitation, in which some services are outsourced at full risk, while others will be reimbursed by the state.
- Primary care case management, under which beneficiaries are assigned to case managers who provide basic medical care and act as gatekeepers, referring patients to specialists when appropriate.

Medicare

Medicare is a federal programme of healthcare for the elderly and disabled. In 2005, the programme is expected to cover 42 million Americans (35.4m seniors and 6.3m disabled) and cost the federal government $325bn. Medicare coverage was originally divided into two parts: Part A, which covers hospital services, along with limited skilled nursing and hospice care, and Part B, which covers physician care and certain other outpatient services. More recently regulators introduced a third part to the program called Medicare Advantage (formerly known as Medicare + Choice). This option enables Medicare beneficiaries to enroll in selected managed care or private fee-for-service plans. Such programmes provide at minimum the same coverage as the original Part B insurance. In addition, they may provide further benefits, such as prescription drug coverage, for the same or a slightly higher monthly premium.

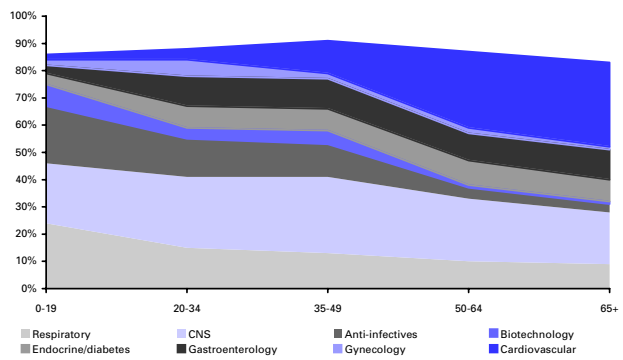
On the inception of the Medicare Act in 1964, outpatient prescription drugs accounted for only a relatively minor component of healthcare and, as such, it was not felt necessary to include their reimbursement within the provisions of the Medicare Act. Since that time, the picture has, of course, changed considerably. Innovation means that medicines now play a much more significant role in healthcare, particularly for the elderly, who are most often those suffering with ailments for which there is a pharmaceutical treatment (e.g. hypertension, diabetes, arthritis, osteoporosis, etc). As shown in Figure 98, under the current programme, some 27% of Medicare beneficiaries do not have drug coverage.

Figure 98: Source of Medicare patient drug coverage 2004



Source: Kaiser Family Foundation

Figure 99: Drug spending by age and therapeutic area



Source: Medco

Medicare drug benefit available from 2006

This apparent inequity has been the subject of much political debate and in November 2003, the US Congress passed the Medicare Prescription Drug, Improvement and Modernisation Act which will introduce an outpatient drug benefit for Medicare beneficiaries from January 2006. The key provisions of this Act are detailed in Figure 100 but several points are worth highlighting:

- **More funding.** The new benefit allocates roughly $400bn over ten years, a significant portion of which will ultimately finance drug purchases. Importantly, as many people who previously were without drug coverage now gain reimbursement for their drug purchases, utilisation is expected to rise. Although this increased role of government as a purchaser of drugs will undoubtedly mean that greater discounts will be extracted from the drug companies, we expect the net effect to be neutral to positive for the industry.
- **Privately managed.** The Medicare legislation relies on private plans to administer the drug benefit, thereby reducing the threat of government price setting. In particular, while the legislation modifies existing pricing restrictions for drugs covered by Medicare Part B (hospital drugs), it leaves the negotiation of prices for medicines covered under the new Part D benefit (outpatient drugs) to the private plans.
- **Tax breaks.** By providing significant tax breaks to employers who offer retiree healthcare coverage, the bill attempts to stall recent declines in such programmes. As these employer-sponsored programmes are often more generous than the provisions mandated by the Medicare drug legislation, the tax breaks should reduce employer incentives to curtail coverage. Thus, healthcare utilisation by covered retirees should see a more limited rate of decline.
- **Dual eligibles**. Importantly, the new drug benefit legislation will transfer coverage of the low-income elderly (so-called 'dual eligibles' who qualify for both Medicare and Medicaid) to the Medicare programme. With the 30% of Medicaid enrollees who are over 65 now coming under the federal system, there will be some relief for stretched state budgets and less need for states to seek cost reductions through other mechanisms such as prior authorization requirements or reduced benefit levels.

Figure 100: Key provisions of Medicare reform legislation

Premium	$35/month
Deductible	$250
Cost-sharing	Medicare provides 75% coverage on first $2,250 of drug spending (after deductible)
Coverage gap	Medicare provides 0% coverage between $2,250 - $5,100 total spending
Catastrophic provision	Medicare provides 95% coverage after $5,100 total spending (i.e., $3,600 out of pocket)
Low-income assistance	Cost-sharing and premium assistance for those up to 150% of federal poverty level (FPL), with no gap in coverage
Dual-eligibles	Dual-eligibles will be covered by the federal Medicare benefit
Means testing	Beneficiaries with incomes >$80,000 (>$160,000 per couple) will be subject to a sliding co-insurance scale, with those in the top income bracket (>$200,000) receiving only 20% Medicare-funded coverage of drug costs.
Benefit design	Beginning in 2006, beneficiaries will have access to at least one Prescription Drug Plan (PDP) and one integrated plan in each region. Two PDPs are required if no integrated plan available. A 'fallback' provision within traditional Medicare will provide coverage in regions where two private plans are not available.
Medicaid best price	Prices negotiated under Medicare Part D are exempt from Medicaid 'best price' determination.
Retiree coverage	Retiree plans offering coverage receive 28% payment for drug costs between $250 and $5,000. This subsidy is tax-exempt.
Private plan competition	Initially, $12bn will be allocated to private managed care plans to encourage them to take on Medicare beneficiaries. From 2010, a comparative pilot programme will begin in six metropolitan areas, where private plans will compete directly with traditional fee-for-service Medicare.
AWP reform	Reimbursement of drugs covered under Medicare Part B will be reduced to 85% of AWP in 2004, and will be reimbursed at average sales price (ASP) plus 6% beginning in 2005. Competitive bidding as a physician choice will be allowed from 2006. The Secretary of HHS has the authority to propose adjustments if ASP is determined not to reflect widely available market prices.
Health Savings Accounts	Creates tax-free Health Savings Accounts (HSAs) where individuals, employers and family members may make contributions and take distributions for medical costs on a tax-free basis.

Source: Committee on Ways and Means AWP = Average wholesaler price

Other federal programmes

Other publicly funded programmes exist. Beyond Medicare and Medicaid, the federal government is also a major purchaser of pharmaceuticals for government-run institutions. Not least among these are the Department of Veterans Affairs, the Defence Department and the Coast Guard. As with Medicaid, discounts are demanded, though at 24% below the average manufacturer's price, the discounts demanded are more onerous. An estimated 20 million people are covered through such schemes.

Europe

The major difference between European and US healthcare is that the majority of European citizens can obtain healthcare benefits from state-organised programmes. In addition, governments in all European nations exert significant control over the cost of care by implementing practices such as price controls on prescription drugs.

Germany

In Germany, statutory health insurance funds (the *Krankenkassen*) cover the healthcare needs of around 90% of the country's 87 million population. Through these funds, those covered have equal access to healthcare benefits from suppliers who are under contract to the national system and who are reimbursed by the funds directly.

For the employed, membership of the insurance system is mandatory unless their income rises above an annually determined threshold. Equal contributions approximating 14% of gross salary are made by both employer and employee and deducted directly from the payroll. For the unemployed or the retired, the government funds this contribution. Those with income exceeding the wealth threshold may choose to have private health insurance coverage instead and account for 8% of the population.

Spiralling welfare costs saw significant reform of the healthcare system in the 1990s as the government endeavoured to contain costs. For the pharmaceutical industry, three measures were of particular significance: reimbursement caps/reference pricing on prescription drugs, generic substitution and the implementation of prescribing budgets.

- **Reimbursement caps/reference pricing:** In 1995, the Federal Ministry of Health introduced a list of recommended pharmaceuticals and prices upon which reimbursements are now based. Prices are determined by therapeutic value, with all drugs in the same therapeutic category reimbursed at the same price.

  The insured pays a fixed contribution for prescribed drugs on the recommended list. The pharmacy is then reimbursed for the remainder by the statutory health insurance system. If the drug is not on the recommended list, the patient will need to pay the entire cost. Consequently, this list is subjected to heated debate and negotiation between the ministry, the doctor's association and the drug manufacturers.

- **Prescribing budgets:** The national prescribing budget for doctors, initiated in 1993, limited the volume and cost of drugs that doctors were allowed to prescribe. Any doctor exceeding his/her budget was subject to financial penalties. Although the use of physician budgets was abolished in 2002, the impact of the directive was to help establish a strong generic market, with doctors tending to prescribe generics as soon as they become available. Generics now account for around 50% of prescriptions in the German market.

- **Generic substitution, or *Aut Idem:*** In late 2001, the German government introduced rules obliging pharmacists to substitute products that were off patent with a generic where available. Doctors are expected to prescribe using the generic name and pharmacists to chose a generic that is among the cheapest available. Doctors can, however, write "not substitutable" on the prescription.

Outside these initiatives, the German government has on regular occasions sought to contain the cost of medicines to the state by introducing obligatory price rebates to the *Krankenkassen*. After a temporary increase to 16% in 2004, the current legislation requires manufacturers to pay a 6% price rebate on all innovative medicines sold to the *Krankenkassen,* together with initiatives to reduce pharmacy and wholesaler margins (both of which will ultimately place further pressure on drug prices).

France

In France, roughly 80% of healthcare costs are covered by Social Security Sickness Insurance (SSSI). This is predominantly financed through compulsory contributions made by employees and employers. The remaining 20% of costs are covered by supplementary private medical insurance and out-of-pocket payments. Out-of-pocket payments are set to increase following the recent implementation of additional cost containment policies in the SSSI schemes.

In an effort to contain overall healthcare costs, the government closely controls the supply of prescription drugs in its capacity as both regulator and the industry's largest customer. Several schemes are implemented:

- **The state SNIP framework agreement**. Introduced in 1994, this provides the framework under which pharmaceutical companies negotiate with the French government on the price, quantity and form of drugs supplied.
- **Pharmaceutical budgets.** The government also agrees on an annual budget with the pharmaceutical companies as to which drugs will be reimbursed and the total level of sales permissible. The drug companies will repay spending in excess of this amount. Most recently, the government reduced its target growth rate for drug spending from 3% in 2004 to 1% for each of the next few years.

In addition, prescription guidelines have been introduced that state which drug is eligible for reimbursement and the reimbursement price. Just over 80% of the prescription drugs currently available are reimbursed by the SSSI schemes. These are subject to several reimbursement rates, depending on the seriousness of the disease treated. Three rates apply:

- 100% for those drugs considered expensive and irreplaceable
- 35% for drugs that treat less serious illness or have weak or moderate therapeutic value
- 65% for the remainder

Most of the working population also purchases supplementary healthcare insurance, which provides cover for that element of cost not reimbursed by the state. Consequently, there is little cost consciousness among a large portion of the population, such that France is the second-largest per capita consumer of drugs in the world after Japan.

Recently, the French government has made significant efforts to stimulate the use of generics. Among other things, initiatives have included agreeing to pay physicians a consultation fee of Euro 20, in exchange for which physicians have consented to write at least 25% of their prescriptions using the generic name. The extent of penetration may, however, be limited by a further decree that limits reimbursement on off-patent branded drugs to the value of the lowest available generic.

United Kingdom

The UK's National Health Service (NHS) was established in 1948 to provide universal healthcare to all residents (58 million). Typically, nationals register with a general practitioner (GP) in their locality. This GP provides general healthcare services but will refer patients to hospital specialists when necessary.

The NHS is financed partly from contributions made by government and partly from national insurance premiums, paid at source by employees and their employers. Employees contribute a fixed percentage of their salary, subject to an annually determined cap. Employers contribute 10% of the employee's gross salary.

Lack of funding in the 1980s led to the reduction of medical budgets and closure of hospitals, with a consequent increase in hospital waiting lists. In part, this has driven a significant increase in the demand for private health insurance. Around 10% of the population currently has some form of private medical insurance in place.

Dispensing of prescription medicines in the UK is either undertaken directly by the GP or, more commonly, through presentation of a GP-written prescription at a pharmacist. For several significant segments of the population, prescriptions are free (e.g., the elderly, students, people on low incomes), with the NHS reimbursing the pharmacist or doctor for the full cost of the drug and paying a fee for dispensation. However, for the majority, a prescription charge of roughly £6.20 is payable per prescription, irrespective of the actual cost of the drug prescribed. This co-payment is used to offset the amount owed by the NHS.

There are a number of drugs that cannot be obtained through the NHS. These are determined by the Advisory Committee on NHS Drugs, which bases its decisions on clinical need, whether an effective existing treatment is already available and the relative cost of the drug. NHS-excluded drugs are detailed on the Selected List, which is updated following each review by the committee. Selected List drugs will not be reimbursed by the NHS.

At the present time, the pharmaceutical bill in the UK corresponds to around 17% of the healthcare budget and continues to increase. The government has sought to contain drug costs in a number of ways:

- **Pricing:** The price that the NHS will pay for any pharmaceutical is determined through negotiation between the Association of the British Pharmaceutical Industry and the Department of Health under the Pharmaceutical Price Regulation Scheme (PPRS) once every five or six years. Under this scheme, each company is allowed to earn a return on capital of 21% for total products supplied. The last PPRS review took place in November 2004, at which time, a 7% price cut was agreed across the industry. The next review is scheduled for late 2009.
- **Usage:** Doctors in the UK are given a voluntary prescription budget under which they are encouraged to consider the cost of medicine prescribed. Unlike the system in Germany, they are not penalised financially for exceeding their budgets. A new body called the National Institute for Clinical Excellence (NICE) was established in April 1999 to review the cost effectiveness of medicines and discourage their use if their cost outweighed their perceived benefits. Given the cost-conscious nature of the UK medical establishment, doctors are unlikely to prescribe medicines highlighted by NICE as cost ineffective. Physicians and pharmacists are also encouraged to substitute generics for branded products where generics are available. Indeed, over 70% of prescriptions are currently written using generic names, while around 55% dispensed are for a generic. Note that this rate of penetration is achieved despite the fact that pharmacists in the UK are not permitted to substitute.

Japan

Japan has a compulsory health insurance system in which everyone living in the country (127 million) must participate. The insured pays insurance premiums to the government and is covered for up to 90% of the cost of medical services and prescription drugs. Costs are determined by the Ministry of Health, Labour and Welfare (MHLW) and set out on the Medical Fee Table (services) and the National Health Insurance Drug Price List (drugs). Some co-payment is invariably required, but the bulk of the cost is paid by one of two government-controlled health insurance programmes.

Individuals either take part in the Employees' Health Insurance plan, or alternatively, the National Public Health Insurance plan if they are not eligible for the employee's plan.

- **Employee's Health Insurance Plan:** This plan is designed for individuals who are in full-time employment. It also covers their dependants. The premium paid equates to 8.4% of salary, paid equally by employee and employer and deducted at source. For the employee, cover runs at 90% of their healthcare costs. For dependants, 70% of outpatient care costs are covered and 80% of any hospital costs.
- **National Public Health Insurance Plan:** Under this scheme, a premium is paid based on the previous year's annual salary and the number of family members insured. Premiums are capped at approximately $4,000 per family. The system covers 70% of the cost of healthcare services or prescription drugs used by the insured and their family.

Japan's healthcare system differs from the US and Europe in that any doctor can both prescribe and dispense prescription drugs. Manufacturers control their market share by supplying prescription drugs to doctors at a discount to the reimbursement price. Because doctors can make a profit from prescribing drugs sold to them at less than reimbursement levels, they have tended to over-prescribe. As a result, Japan is the largest consumer of drugs per capita, with pharmaceuticals representing over 20% of total healthcare costs.

In response to this apparent abuse of the system, the Japanese Health Ministry has been reducing the reimbursement price for pharmaceuticals since the 1980s, so reducing doctors' margin and discouraging over-prescription and manufacturer discounts. This has seen some success. Recommendations to further improve the system are ongoing.

Government measures to curb rapid expansion

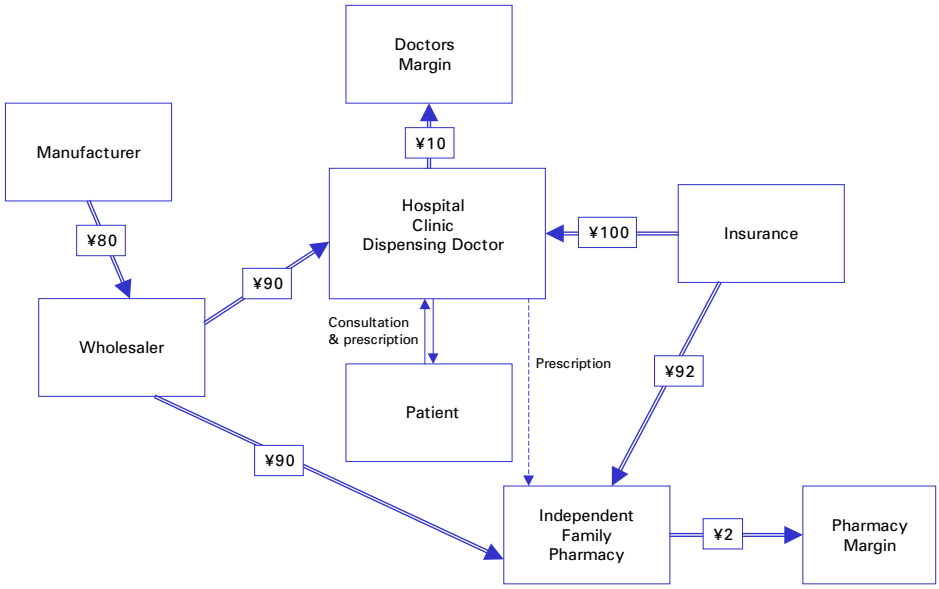
The Japanese government, increasingly concerned at the prospect of drug and healthcare costs spiralling out of control, some time ago initiated a series of measures designed to eliminate the financial incentive to overprescribe.

Bungyo – The separation of prescribing and dispensing pharmaceuticals

One measure was *Bungyo,* the separation of prescribing and dispensing of prescriptions by promoting the filling of prescriptions by independent health insurance or 'family' pharmacies rather than allowing the prescribing physician also to dispense the drug. *Bungyo* was first introduced in 1974 but was not aggressively pursued by the MHLW until 1992, with the implementation of the Bungyo Promotion Programme.

Bungyo reduces the financial drivers in prescribing, as independent pharmacies only fill prescriptions and obtain very little discount from drug companies. They do, however, enjoy higher dispensing fees than a dispensary within a clinic. As justification, and perhaps so as not to completely alienate dispensing physicians, the ministry cited patient-related benefits attributable to *Bungyo* and the dispensing of prescriptions by independent family pharmacies. These included better patient knowledge of the drug prescribed and greater continuity of information about those drugs, a reduced potential for overlapping treatment regimes and drug interactions, which can be seen if a patient consults more than one doctor at different clinics, and increased patient compliance.

Figure 101: Bungyo – The separation of prescribing and dispensing



Source: MHLW, Japanese Pharmaceutical Association, Deutsche Bank research

As can be seen in Figure 101, a patient attending a hospital, clinic or a prescribing physician will incur an eventual cost for the insurance company of ¥100, including a doctor's margin of ¥10. However, when a patient has a prescription dispensed at an independent pharmacy, the margin is significantly reduced. Interestingly, when drug prices are also reduced, as they have been in Japan on a regular basis, the official list price often falls more than the wholesaler price. This also squeezes the doctor's margin.

The government has met with some success in its *Bungyo* endeavours. In 1970, the number of prescriptions received by independent health insurance pharmacies was only 4.7 million. However, this spiralled to around 400 million in 1998, as the *Bungyo* promotion programme became increasingly effective. Moreover, the *Bungyo* rate, the proportion of out-patient prescriptions dispensed by independent pharmacies, has increased from only 9.7% in 1986 to 30.5% in 1999, although large regional variations do occur. A *Bungyo* rate of 100%, though most unlikely to occur as hospitals and clinics will always continue to dispense drugs, would indicate complete separation of prescribing and dispensing. Today, the Bungyo rate is estimated to stand at over 50%.

The R-Zone and regular price decreases

The government also stepped up pressure on excessive market growth and on drug discounts by introducing the R-Zone, a level of discount on prices it believed to be 'reasonable.' If discounts in excess of this level were being obtained, then price decreases would be implemented in an attempt to contain rising costs and also to restrict the doctor's margin on prescriptions. Price cuts continued biennially throughout the early 1990s and are expected to continue every other year for the time being.

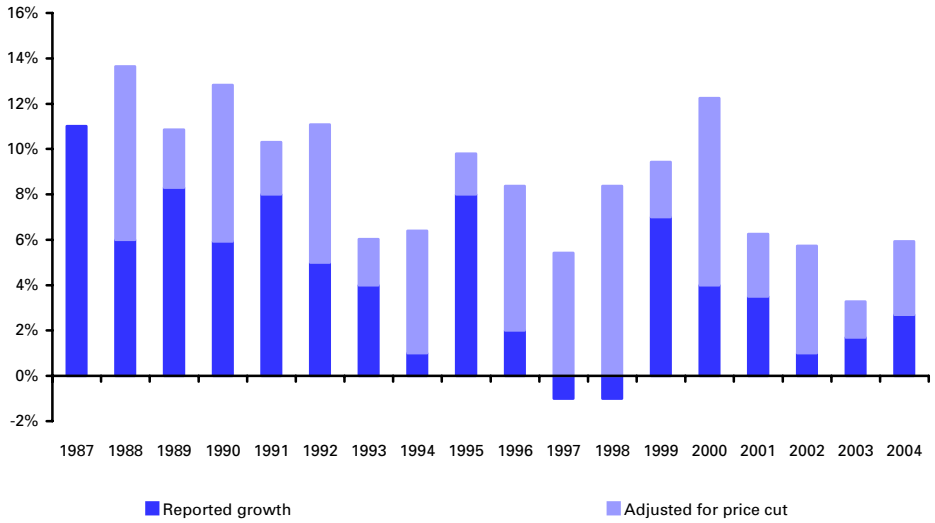
Figure 102: Japan – A decade of price cuts (%)

	1988	1990	1992	1994	1996	1997	1998	2000	2002	2004
Price Cut	-10.2	-9.2	-8.1	-7.2	-8.5	-4.4	-9.7	-11	-6.3	-4.3

Source: Ministry of Health, Labour & Welfare

Aside from price reductions, the MHLW has also used an increase in co-payments as a means of containing the cost of medicines. Thus, having introduced co-payments for salaried workers of 20% in 1997, in October 2002, a 10% basic co-payment was introduced for the elderly (20% for those above a certain income threshold). This was followed in April 2003 by a further 10% increase in the co-payment made by salaried employees. As illustrated below, co-payments combined with price cuts have significantly held back the value growth of the Japanese market since their introduction in the 1980s.

Figure 103: Growth rates in Japan adjusted for price cuts



Source: IMS, MHLW

US patent litigation

Given the increasing frequency of early patent challenges in the pharmaceutical sector, we have provided in this section an overview of key US patent legislation and the litigation process in order to provide a framework by which to understand and follow the progression of ongoing lawsuits.

Legal standards for patentability

According to US patent law, in order for an invention to be patentable, it must be both novel and non-obvious. These requirements are set forth in Title 35 of the United States Code (USC), Sections 102 and 103 (see Figure 104).

Novelty

In order for a patented product to be considered novel, it must not have been previously described in a form of prior art. Prior art is defined under Section 102(a) of the statute as public knowledge that was known and available before the invention by the patentee. Section 102(b) places emphasis on the timing of a patent filing and requires that the patentee file an application within one year of describing the invention in a written publication.

In legal terms, a patent claim is said to be 'anticipated' if the claimed invention is found to be substantially the same as that described in a prior art reference. Determination of anticipation requires a two-step analysis:

- claim construction of the challenged claims (a question of law), and
- determination of whether a single prior art reference contains each and every element of the challenge claims (a question of fact).

Importantly, the standard for proving anticipation is rigorous and if a court must look beyond a single prior art reference (considering both specific and inherent claims), the proper legal challenge should be obviousness, not anticipation. In addition, the prior art reference must be 'enabling', that is, it must contain 'a substantial representation of the patented improvement in such full, clear and exact terms as to enable any person skilled in the art or science to which it appertains to make, construct and practice the invention to the same practical extent as they would be enabled to do if the information was derived from a prior patent'. *Seymour v. Osborne*, 78 U.S. (11 Wall.) 516, 20 L.Ed.33 (1870).

Non-obviousness

The second key element required for patenting is non-obviousness. Under 35 USC 103, if the differences between the invention and the prior art are such that the invention would have been obvious at the time it was invented to a person having ordinary skill in the art, then it would be considered obvious and would not be patentable.

Figure 104: US patent legislation – 35 USC 102 and 103

35 USC 102 (Novelty)

(a) A person shall be entitled to a patent unless – the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent.

(b) A person shall be entitled to a patent unless – the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States.

35 USC 103 (Non-obviousness)

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

(b) (1) Notwithstanding subsection (a), and upon timely election by the applicant for patent to proceed under this subsection, a biotechnological process using or resulting in a composition of matter that is novel under section 102 and nonobvious under subsection (a) shall be considered nonobvious if –

(A) claims to the process and the composition of matter are contained in either the same application for patent or in separate applications having the same effective filing date; and

(B) the composition of matter, and the process at the time it was invented, were owned by the same person or subject to an obligation of assignment to the same person.

(2) A patent issued on a process under paragraph (1)

(A) shall also contain the claims to the composition of matter used in or made by that process, or

(B) shall, if such composition of matter is claimed in another patent, be set to expire on the same date as such other patent, notwithstanding section 154.

(3) For purposes of paragraph (1), the term ''biotechnological process'' means –

(A) a process of genetically altering or otherwise inducing a single- or multi-celled organism to – (i) express an exogenous nucleotide sequence, (ii) inhibit, eliminate, augment, or alter expression of an endogenous nucleotide sequence, or (iii) express a specific physiological characteristic not naturally associated with said organism;

(B) cell fusion procedures yielding a cell line that expresses a specific protein, such as a monoclonal antibody; and

(C) a method of using a product produced by a process defined by subparagraph (A) or (B), or a combination of subparagraphs (A) and (B).

(c) Subject matter developed by another person, which qualifies as prior art only under one or more of subsections (e), (f), and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person

Source: US Code

The original test for obviousness was set forth in a Supreme Court decision, *Graham v. John Deere Co.,* 383 U.S. 1 (1966), in which the Court required consideration of three factors:

- the scope and content of prior art,
- the differences between the prior art and the claims at issue, and
- the level of ordinary skill in the pertinent art.

Subsequent litigation in the Federal Circuit Court, *B.F. Goodrich Co. v. Aircraft Braking Systems Corp.,* 72 F.3d 1577, 1582 (Fed.Cir.1996) and *Hybritech, Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d 1367 (Fed. Cir. 1986) has expanded this definition to include a fourth factor:

- secondary considerations, if any, of non-obviousness, which may include but are not limited to: a) the commercial success of the invention, b) whether the invention satisfied a long-felt need in the industry, c) failure of others to find a solution to the problem at hand, and d) unexpected results.

Again, it is important to note that there must be a motivation to combine the insights provided in the various prior art references in order to render an invention obvious. This 'reason, suggestion or motivation' must derive from the references themselves, knowledge of those skilled in the art, or 'the nature of the problem to be solved, leading inventors to look to references relating to possible solutions to that problem'. *Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc.,* 75 F.3d 1568, 37 USPQ2d 1626 (Fed. Cir. 1996).

Moreover the courts have cautioned against using hindsight in making a finding of obviousness. In *Rockwell Int'l Corp v. United States*, 147 F.3d 1358, 47 USPQ2d 1027 (Fed. Cir. 1998), the court indicated that it was inappropriate to use the patent in suit 'as a guide through a maze of prior art references, combining the right references in the right way so as to achieve the results of the claims at suit.' In addition, the mere disclosure of a multitude of possibilities (e.g., a broad class of chemical compounds that may be useful in producing a desired therapeutic effect) but without a suggestion as to which of the possibilities is likely to be successful, should not invalidate a claimed invention simply because the inventor could have tried each of the numerous possibilities until he or she eventually arrived at a successful result.

Inequitable conduct

Although there are other requirements set forth in US patent law, the most common avenues for patent challenges relate to prior art and obviousness. While a generic company could also challenge a patent, for example, by arguing that one of the original inventors was not named on the application under 35 USC 102 (f), such arguments are generally weak unless they are proven to be a result of willful misconduct on the part of the patentee.

That said, most parties wishing to challenge a patent's validity will argue that the patentee committed inequitable conduct by intentionally misleading the Patent Office. While such inequitable conduct claims are among the most difficult to prove, they are often included in litigation because the entire patent is rendered invalid if the patentee is found guilty. This is in contrast to arguments of anticipation or obviousness, which must be proven claim by claim.

In order for a court to find a patentee guilty of inequitable conduct, it must determine that the patentee misled the Patent Office by intentionally misrepresenting or omitting a fact that the reviewer would have considered material in his or her review. This requires a finding of both materiality and intent. However, because of the difficulty in proving both of these issues and given the severe penalty associated with a guilty ruling (i.e., full patent invalidity), findings of inequitable conduct are generally uncommon.

The US litigation process

Initial proceedings: The complaint and answer

When an innovator company wants to claim infringement of its patents, it files a 'complaint' with one of the federal District Courts. (According to US law, the federal District Courts have exclusive jurisdiction for all patent litigation.) The complaint describes the company's alleged injury (patent infringement) and how the defendant caused the injury (filing of an ANDA with an intent to launch). It also makes a specific request for relief (e.g. an injunction preventing launch) and/or damages. This action triggers the 30-month Hatch Waxman stay described in the previous section.

The generic firm must next file its 'answer' in which it admits or denies the plaintiff's allegations. In addition, the defendant may assert 'counterclaims' in which it argues, for example, why the plaintiff's patents should be ruled invalid. It is important to note, however, that the pleading in the US federal courts is 'notice' pleading. This means that each party merely provides enough information in the complaint, answer and any counterclaim to put the other side on notice of its claims. More factual detail is gathered through the discovery process that follows.

In these early stages, the branded company may request a jury trial as historical precedent suggests a greater probability of patents being upheld when considered by a jury versus judge. In most cases, however, the court will deny this request, leaving the presiding judge to render the decision. (Although the US Constitution guarantees the right to a jury trial, it

requires that damages be in excess of $20. But as patent lawsuits usually precede the launch of generic products, at the time of trial there are typically no damages yet accrued.)

Discovery

The next phase of litigation is the discovery process. During discovery, the litigants will obtain information from one another through the use of depositions (testimony under oath), interrogatories (lists of pointed questions) and requests for documents. While some of these requests may raise concerns over the disclosure of proprietary information, trade secrets, etc, each party is required to provide such information if it is admissible in court or is likely to lead to admissible evidence. However, there may be interim disputes that must be resolved by the court when one party refuses to disclose information to the other.

Discovery is the most time-consuming and expensive part of the litigation process and usually takes many months if not years. For example, in the patent litigation surrounding Sanofi-Aventis' Plavix, discovery did not complete until some 18 months after the case was initially filed.

Claims construction (the Markman hearing)

A key element of patent litigation is the claims construction hearing. During the claims construction process, the court will rule on the interpretation, and thus the scope, of the patent claims. For example, regarding the claim in Sanofi's '265 patent for Plavix that describes a dextro-rotatory isomer 'substantially separated' from the levo-rotatory isomer, the court might specify what percentage purity is implied by the phrase 'substantially separated'. (This process is often referred to as the 'Markman' hearing following a Federal Circuit decision, later affirmed by the Supreme Court, in *Markman v. Westview Instruments,* 52 F.3d 967 (Fed. Cir. 1995) in which the Court determined that the interpretation of patent claims was a matter to be decided by the judge and not the jury.)

In making its decision, the court will consider the written patent description and drawings along with the patent prosecution history. In addition, the court may consider 'extrinsic' evidence (i.e., information not specifically described in the patent documentation) if it is necessary to help the court understand the underlying technology or to find the ordinary meaning of a disputed term. Yet, the focus must remain on the meaning of the claim language itself, and extrinsic evidence cannot be used to explain away ambiguity or vary the claim terms. As stated in the Markman opinion, 'the invention protected by the patent must be covered by the claims, otherwise it is lost.'

Summary judgment

Following the claims construction hearing, either of the litigants may file a motion for summary judgment with the court. A motion for summary judgment asserts that there is no 'genuine issue as to any material fact' and that the moving party is entitled to judgment as a 'matter of law'. *Anderson v. Liberty Lobby,* 477 US.242 (1986). That is, the moving party will argue there is no need for a trial because the facts (including those gathered in discovery, the pleadings and any affidavits) are not in dispute between the two parties.

In pharmaceutical patent cases, generally it is the generic company, if anyone, that files such a motion. In contrast, the branded company is typically content to let the legal process – and thus the continued freedom from generic competition – drag on as long as possible. For a drug with significant sales, the cost of a few additional months of legal fees is typically less than the potential profits that would be lost if there were an early generic launch.

Resolution of a summary judgment motion is rarely a straightforward determination, however, and both parties will submit briefs explaining why they believe there are or are not outstanding questions of fact that should be left for consideration at trial. In addition, because

there are often multiple issues involved, it is not uncommon for a judge to grant summary judgment on some claims but not on others.

Pre-trial hearing and order

The next key event in the litigation process (assuming the case has not been decided by summary judgement) is the pre-trial hearing, during which the judge and attorneys meet to plan the framework of the trial. The court will subsequently issue a pre-trial order confirming the matters addressed in the pre-trial conference, which may include the nature of the case, the theories of the parties, the admitted facts, the facts in dispute and the list of witnesses and exhibits to be introduced at trial. In addition, the court will at this time set the trial schedule.

The trial

Some one to three years (on average) after the start of litigation, the case will come to trial. If the case is heard by a jury, the verdict will be rendered at the end of the trial. After a bench trial, however, the parties may, either on their own initiative or at the request of the court, submit post-trial briefs in which they argue for a set of findings of fact and conclusions of law that they want the court to adopt. Thereafter, the court may deliberate several weeks or months before issuing its written opinion.

The appeals process

If either party is unsatisfied with the District Court's verdict, it may appeal the case to one of the 12 regional Courts of Appeals or to the Federal Circuit Court of Appeals. The 'appellant' (the party appealing the decision) must initiate the appeal within 30 days of the lower court decision by filing a Notice of Appeal with the District Court. Thereafter, the appealing party will submit a written brief in which it argues that the lower court erred in its decision. The other party, the 'appellee', will respond with a similar brief and may, if it was displeased with certain parts of the decision, elect to cross-appeal. The appellant then has the final word in a reply brief filed with the court.

Appeals cases are heard by a panel of three judges (who are often better-versed in patent litigation than the District Court judges). The panel will have received a copy of the parties' briefs and will subsequently hear short (15-30 minutes on average) oral arguments from each of the litigants.

It is important to emphasise that the authority of the appellate court is limited. The court is not permitted to receive new evidence or hear witnesses, and rather relies upon the factual findings of the lower court and the transcript of the trial. It can only overturn these findings if they are determined to be 'clearly erroneous', meaning that a reasonable person could not reach the factual conclusion of the lower court based on the evidence presented at trial.

Instead, the primary focus of the appellate court is on questions of law and whether the lower court correctly applied the law. If it determines that the lower court erred in its application, it can decide to reverse the lower court's decision. However, if the application of the law involves a judgement because the law itself is unclear, the appellate court may not substitute its judgement for that of the lower court.

Many months may pass before the Court of Appeals issues a decision. This decision may simply be an affirmation or reversal of the original verdict or it may include a request that the case go back to the lower court for resolution of some matter. (For example, if a District Court granted a preliminary injunction preventing a generic company from launching its product and the appellate court overturned the injunction, the patent case would return to the lower court for further litigation.) Note that the decision by the Court of Appeals is binding on the parties, and to the extent it decides new legal premises, is binding on parties within that Circuit.

Finally, a litigant dissatisfied with the appellate decision may file a petition for a 'writ of certiorari' – a document asking the US Supreme Court to review the case. The initiating party, now known as the 'petitioner', files a brief supporting its request for review and the opposing party, the 'respondent', files a brief opposing review. If the petition for certiorari is granted, the parties will file briefs similar to those filed in the Court of Appeals.

Review by the Supreme Court is discretionary, however, and is granted for only a tiny fraction of cases that involve an unusually important legal principle, or when two or more federal appellate courts have interpreted a law differently. If review is granted, the parties will file further briefs and argue their case before the nine Supreme Court justices. The Court will subsequently issue a written decision sometime before the end of the Court's term in June. This decision becomes the 'law of the land' and is binding on the parties and all other persons.

US legislative process

Given the importance to the pharmaceutical industry of the changing US legislative landscape, we thought it useful to include a brief description of the US legislative process in this document. This may, for example, help readers follow the progress of any medical reform legislation in this and future sessions of Congress.

Law-making in the United States

The process for a bill to become law in the US is often a long and complicated process, replete with procedural rules and loopholes. According to the US Constitution, legislative responsibility falls to Congress. The US Congress is divided into two separate but equal bodies, the House of Representatives and the Senate. The House comprises 435 members, elected every two years. The Representatives are apportioned to the populations of each of the 50 states. The Senate comprises 100 members – two from each state. Senators are elected to terms of six years, with one-third of the total membership of the Senate elected every other year. Each 'Congress' lasts two years and is divided into a First and Second session. The 109th Congress began its term in January 2005.

Figure 105: Composition of 109th US Congress (2005-2007)

House of Representatives*	Senate
231 Republicans	55 Republicans
202 Democrats	44 Democrats
1 Independent	1 Independent

*Source: US House of Representatives, US Senate *1 vacancy as of June 2005*

Types of legislation

Ideas for new legislation may arise from a variety of sources – from the members of Congress, from individuals or citizen groups, from a member of the President's Cabinet or from the President himself. Once an idea is conceived, a member of Congress must introduce the draft legislation into his or her respective house.

There exist four principal forms of legislation: the bill, the joint resolution, the concurrent resolution and the simple resolution. The most common of these is the bill, of which there were around 8,500 introduced in the 108th Congress. Bills may be introduced in either the House or the Senate, with the exception of bills for raising revenue. These must originate in the House. By tradition, general appropriation bills also originate in the House. Bills may be 'public', affecting the general population, or 'private', affecting a specific individual or private entity. The term 'companion bill' is also used to describe a bill introduced by one chamber of Congress that is similar or identical to a bill under consideration by the other chamber.

There is little practical difference between a joint resolution and a bill. Like a bill, a joint resolution may be introduced in the House or the Senate but not jointly in both houses, as often assumed. They are subject to the same approval procedure as bills, with the exception of a resolution proposing a constitutional amendment. In such cases, the resolution must be approved by two-thirds of the House and the Senate and ratified by three-quarters of the states. It is not reviewed by the President.

Concurrent and simple resolutions are used for regulating the operations of one or both houses. Concurrent resolutions affect the operations of both houses, whereas simple resolutions affect only the House or the Senate. To be effective, each resolution must be approved only by the relevant house(s).

Introduction and referral to committee

For the purpose of simplicity, we will focus on the legislative pathway for a bill introduced in the House, as most of the process is the same for one originating in the Senate. Any member or group of members may introduce a new bill or joint resolution. Upon introduction, the bill is referred to the appropriate committee with jurisdiction over its subject matter. This is perhaps the most important phase of the legislative process, as the committees hold primary responsibility for scrutinising the bill. In fact, only a small percentage of bills ever make it past committee.

Currently, there are 19 standing committees in the House and 16 in the Senate, in addition to several select or special committees. Each of these committees is further broken down into subcommittees. Healthcare matters fall under the jurisdiction of the Committee on Energy and Commerce in the House and the Committee on Health, Education, Labour and Pensions in the Senate.

Membership of committees is divided between the two major political parties. By custom, the division approximately reflects the split in the house as a whole. Each of the two parties initially assigns its members to committees, with the final slate being approved by the full chamber. Each committee also elects as chairman a member of the majority party.

During the review process, the subcommittee solicits opinions from the relevant government agencies and non-government experts. The bill is then amended during a so-called 'mark-up' session, after which the subcommittee may decide to report a favourable, an unfavourable or no recommendation to the parent committee. The subcommittee may also recommend tabling the bill indefinitely. A similar process follows in the full committee. However, the parent committee also may vote on the measure and forward it to the whole House.

Motion to discharge committee

Occasionally, the committee process may be circumvented by what is known as a 'discharge petition'. If a bill has been held up by a committee for at least 30 days, or if the Committee on Rules refuses to clear it for floor action within seven days, any member may offer a motion to discharge the committee from the bill. A simple majority is required to pass the motion. While discharge petitions are seldom successful – members are reluctant to disregard the committee judgement and review process – the threat of such a move may spur a committee to act.

Committee recommendation to the House

If the committee votes to report the bill to the House, it drafts a report describing the purpose and scope of the bill and the reasons for approval. The report will highlight any areas of existing law the bill proposes to change. It will also state all amendments to the original draft. (These reports often serve as the most valuable resource in understanding the history of a law and are frequently referenced by courts and executives.)

When a public bill is favourably reported to the House, it is assigned a calendar number on the Union or House Calendar. The Union Calendar includes all public bills regarding the raising of revenue or the appropriation of money or property. All other public matters are scheduled on the House Calendar.

All measures on the Union Calendar must first be considered by the Committee of the Whole House, an abbreviated version of the full House that requires only 100 members for a quorum. This committee debates and amends legislation but cannot pass a bill. Rather, all bills considered by the Committee of the Whole or listed on the House Calendar must undergo debate and passage by the full House. A simple majority is required for passage.

Passage of the bill to the Senate

Upon approval by one house of Congress, the bill moves on to the other house for consideration. Thus, a House resolution is passed to the Senate. In the Senate, the bill undergoes roughly the same process as it did in the House, including the same detailed review in committee and subcommittee. However, if the bill is of a non-controversial nature, the Majority Leader may ask for unanimous consent for immediate consideration and order a vote with little or no debate.

One of the key differences in the Senate proceedings is that there is no fundamental 'germaneness rule'. Whereas in the House, any proposed amendment must be germane to the underlying bill, Senators may try to introduce legislation by tagging their amendment onto unrelated bills being debated on the Floor.

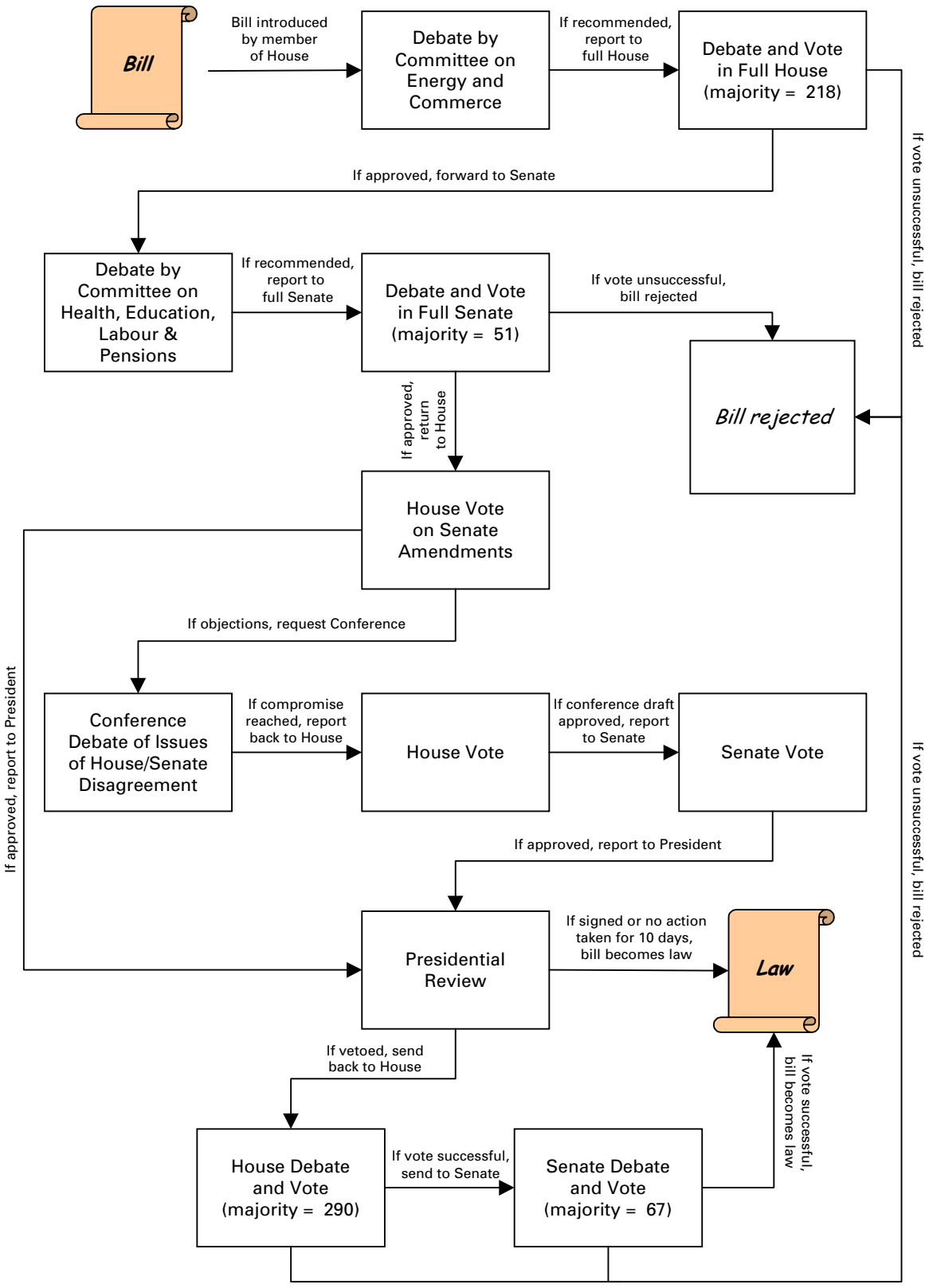
Resolution of disagreements

Following Senate approval, the bill, engrossed with new amendments, returns to the House. If there are no objections to Senate amendments, the bill is immediately presented to the President. In the event of disagreements, the originating house may request a conference. Conferees, which include members from each house (generally members of the relevant committees), are strictly limited in their consideration to matters in disagreement. If the conferees reach a compromise, the bill must again be voted on and approved by both houses. Only after a bill has been passed in identical form by the House and Senate may it be presented to the President.

Presidential approval or veto

Once approved by the legislature, the bill is given to the President. The President has three options: 1) he may sign it into law, 2) he may do nothing, whereby after ten days (excluding Sundays), the bill automatically becomes law, or 3) he may veto it. If the bill is passed via either of the first two options, it becomes law immediately, unless the bill expressly specifies a different date. In the event of a veto, Congress may override the decision if both houses achieve a two-thirds majority in favour of the bill. However, if the vote is unsuccessful, the bill is rejected.

Figure 106: US legislative process (example of House-sponsored Healthcare Bill)


Bill
Bill introduced by member of House
Debate by Committee on Energy and Commerce
If recommended, report to full House
Debate and Vote in Full House (majority = 218)
If vote unsuccessful, bill rejected
If approved, forward to Senate
Debate by Committee on Health, Education, Labour & Pensions
If recommended, report to full Senate
Debate and Vote in Full Senate (majority = 51)
If vote unsuccessful, bill rejected
Bill rejected
If approved, return to House
House Vote on Senate Amendments
If objections, request Conference
If approved, report to President
Conference Debate of Issues of House/Senate Disagreement
If compromise reached, report back to House
House Vote
If conference draft approved, report to Senate
Senate Vote
If approved, report to President
Presidential Review
If signed or no action taken for 10 days, bill becomes law
Law
If vetoed, send back to House
House Debate and Vote (majority = 290)
If vote successful, send to Senate
Senate Debate and Vote (majority = 67)
If vote successful, bill becomes law
If vote unsuccessful, bill rejected

Source: Deutsche Bank

Legislative dictionary

Act - Legislation that has passed both chambers of Congress in identical form and signed into law. Also refers to a bill that has been passed by one house.

Amendment in the nature of a substitute - An amendment that strikes out the entire text of a bill and inserts a different full text.

Bill - Draft legislation introduced by either the House or the Senate, not yet enacted into law. Designated H.R. and S.R. followed by a number, for House and the Senate bills, respectively. Similar in function to a joint resolution.

Calendar of Business - One of the two calendars of the Senate, covering all public and private bills and resolutions.

"Clean Bill" - A new bill (with a new number) that encompasses in a clean draft the text of a previous bill, including all amendments. Designed to expedite legislative action by avoiding separate floor consideration of each amendment.

Cloture - A Senate motion to limit the length of debate on a particular bill, in order to prevent filibustering. Requires three-fifths vote for passage.

Committee of the Whole – Essentially, the full House operating under a different set of rules that requires only 100 members (instead of 218) for a quorum. Permitted to debate and amend, but not pass legislation.

Committee on Rules - Reports special rules that set the terms for debate and amendments on specific measures.

"Companion Bill" - A bill or resolution introduced by one house that is similar or identical to legislation introduced by the other. Intended to promote simultaneous consideration of a measure.

Concurrent resolution - A measure used to deal with matters affecting both houses of Congress. Designated H. Con. Res. or S. Con. Res. for House and Senate resolutions, respectively. Does not require presidential approval.

Conference - A temporary panel of House and Senate representatives convened to resolve disagreements on a bill that has passed through both chambers.

Corrections Calendar - One of the calendars of the House, containing resolutions eligible for expedited passage. Matters are generally specific, non-controversial issues or narrowly targeted bills. Passage from this calendar requires a three-fifths majority.

Discharge Calendar - The calendar of motions to discharge committees from consideration of certain public bills or resolutions.

Engrossed Bill - The official copy of a bill or resolution passed by the House or Senate.

Enrolled Bill - The final copy of a bill or resolution passed by both chambers in identical form. Printed on parchment paper, signed by House and Senate officials, and submitted to the President for signature.

Executive Calendar - One of the two calendars of the Senate, covering treaties and nominations.

Filibustering - Excessive Senate debate and/or procedural motions intended to block or delay action on a particular bill.

Germaneness rule - A rule in the House preventing the proposal of irrelevant amendments. No such requirement exists in the Senate, allowing for the addition of unrelated amendments, often called "riders".

House Calendar - The second of the two primary legislative slates of the House. Includes all public bills that do not raise revenue or appropriate money or property.

Joint resolution - Draft legislation introduced by either the House or the Senate, not yet enacted into law. Designated H.J. Res. and S.J. Res. followed by a number, for House and the Senate resolutions, respectively.

Majority/Minority Whips - Act as Senate floor leaders in the absence of Majority/Minority Leaders. Often responsible for rallying party votes on major issues.

Motion to discharge committee - A motion to discharge a committee from the consideration of a public bill or resolution that was referred to the committee 30 days prior thereto. Requires a majority vote for passage.

Motion to recommit/reconsider - A motion to reconsider a question already decided by vote. Rules generally permit one motion to reconsider any issue. Usually offered by a supporter of the outcome immediately after the vote, followed by another motion by the same Senator (or other supporter) to table the motion, thus securing the outcome of the vote.

Motion to suspend the rules - A motion to bypass usual procedure and bring a matter before the House for immediate consideration and passage. Generally proposed for routine legislation perceived to have a broad degree of support.

"Pocket Veto" - A veto that occurs indirectly, because Congress has adjourned before the end of the President's ten-day window to take action on a bill.

Point of order - A claim that a rule of the House or Senate has been violated.

President of the Senate - Presiding officer of the Senate, officially, the Vice President. They may (but are not required) to vote in the case of a tie. Duties performed by the President Pro Tempore (and others designated by him) during the Vice President's frequent absences.

President Pro Tempore - Constitutionally appointed officer who presides over the Senate in the absence of the Vice President. By custom, the Senator of the majority party with the longest record of continuous service.

Private Calendar - A legislative slate of the House that includes all bills and resolutions relating to a private matter.

Quorum - The number of members required to do business – generally, a simple majority (218 in the House, 51 in the Senate).

Senate Majority/Minority Leaders - Elected by their respective parties to serve as chief Senate spokespeople and to manage and schedule the legislative and executive business of the Senate.

Simple resolution - A measure used deal with matters affecting only one house of Congress. Designated or H. Res. or S. Res. for House and Senate resolutions, respectively. Does not require presidential approval.

Speaker of the House - Member of the majority party who serves as presiding officer of the House. Traditionally refrains from debating or voting and does not sit on any standing committees. Second in line to succeed the President.

Time agreements - A motion in the Senate to limit the time for debate, specify speakers and/or control the addition of amendments. Requires unanimous consent for approval.

Union Calendar -The first of the two primary legislative slates of the House. Includes all public bills appropriating money or property or authorising an undertaking by a governmental agency that will incur an expense to the government.

Veto - Rejection of a bill or resolution by the President. Usually returned to the originating house, stating objections. May be overridden by a two-thirds majority vote of both the House and Senate.

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Diabetes mellitus

- Worldwide market, including insulin, in 2004 worth around $13bn
- Prevalence of diabetes estimated at 194 million people worldwide
- New products driving double-digit growth
- Leading companies include Novo, Lilly, Sanofi-Aventis, GlaxoSmithKline

Diabetes mellitus is estimated to affect over 5% of the population in the developed world. In North America alone, over 21 million people suffer from the disease, although only an estimated 65% are diagnosed. In today's society, where obesity and a sedentary lifestyle are growing in prevalence, the incidence of diabetes is said to be increasing at a rate of about 5% per annum. In addition to those who actually suffer from the disease, a further 50 million worldwide suffer from impaired glucose tolerance (IGT), many of whom will ultimately need treatment.

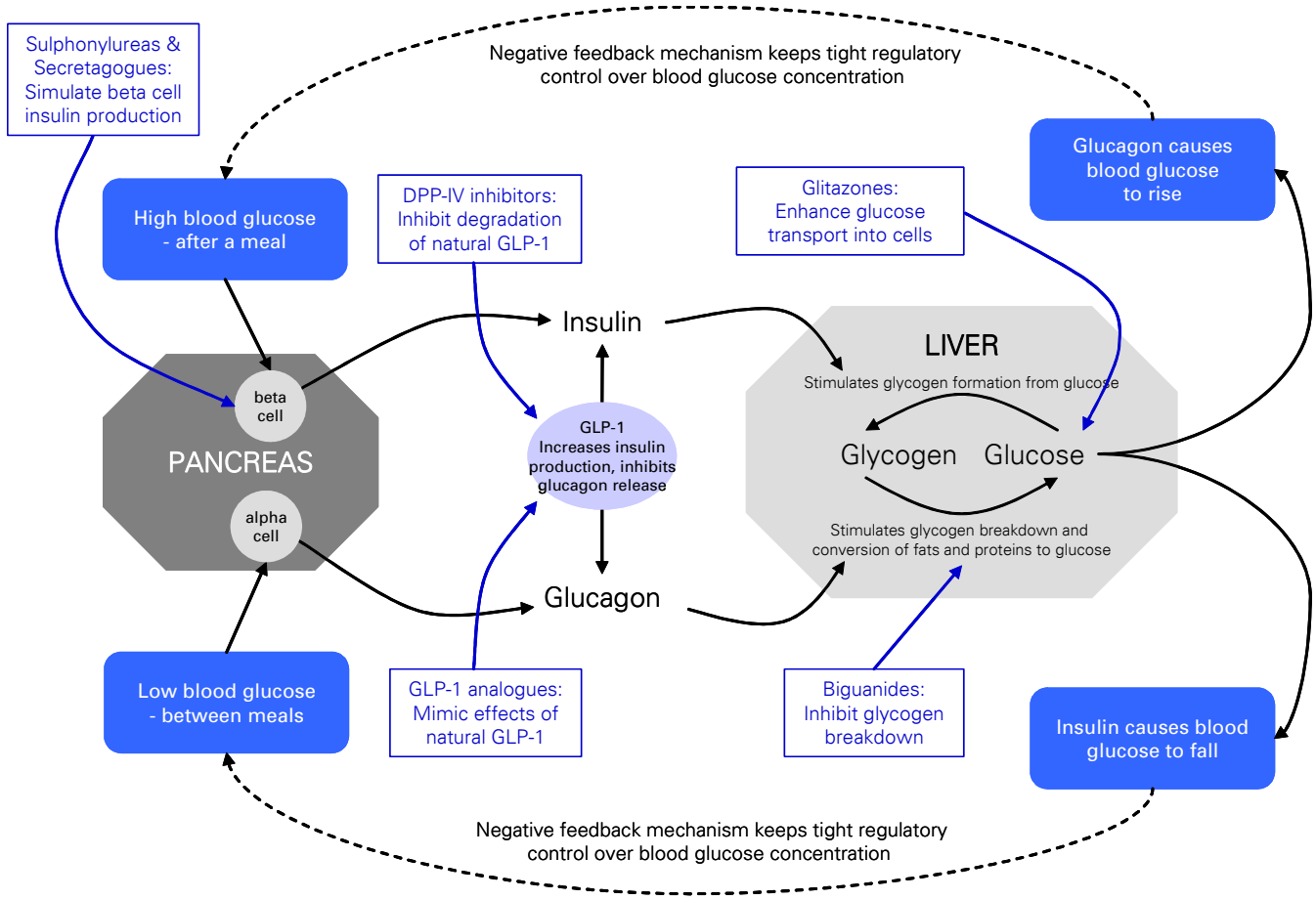
Physiology

Diabetes is a chronic metabolic disorder characterised by poor blood glucose control due to insulin deficiency and/or insulin resistance. Glucose is the primary fuel of cells. In healthy individuals, two principal glucose-regulating hormones – insulin and glucagon – maintain a constant glucose concentration in both the fasting and post-meal (post-prandial) state. When blood glucose levels are abundant, such as after eating a meal, insulin is released. Produced by cells in the pancreas, called beta cells (see diagram), it acts to encourage the uptake, utilisation and storage of glucose in muscle and fat tissues, but mainly in the liver. During fasting, insulin output falls and, among others, a counter regulatory enzyme, glucagon, is released. Also produced in the pancreas but by alpha cells, glucagon stimulates the release of glucose into the blood from the liver by breaking down glucose stores called glycogen and converting other fuel sources such as fats and proteins.

In a healthy body, blood glucose levels rise and fall within a fairly tight range of 70-110mg/dl. However, with diabetic insulin deficiency and/or resistance, blood glucose can rise to substantially higher concentrations, resulting in hyperglycaemia and, in the long term, causing blindness and damage to the kidney and heart, among other organs. There are two types of diabetes mellitus:

- In Type 1 diabetes, or insulin-dependent diabetes, there is an absolute shortage of insulin resulting from destruction of the insulin-producing beta cells by the patient's own immune system. Accounting for roughly 10% of cases, Type 1 diabetes sufferers are typically young. Given Type 1 patients' inability to produce insulin, treatment inevitably includes supply of exogenous insulin.
- Type 2 accounts for roughly 90% of cases and occurs predominantly in people over 40. In over 60% of reported cases, patients are overweight. The disease is most often characterised by a resistance of the peripheral tissues to insulin and impaired regulation of insulin secretion. Consequently, Type 2 diabetes is also known as non-insulin dependent diabetes mellitus (NIDDM); that is, insulin is produced but the body's insulin receptors are insufficiently sensitive to its presence. As a result, the insulin producing beta cells over-compensate for this poor sensitivity, with the frequent result that, over time, they 'burn out'. Hence, insulin production gradually deteriorates, with around 30% of patients eventually becoming insulin dependent.

Figure 107: Blood glucose is controlled by insulin and glucagon


Sulphonylureas & Secretagogues: Simulate beta cell insulin production
Negative feedback mechanism keeps tight regulatory control over blood glucose concentration
Glucagon causes blood glucose to rise
High blood glucose - after a meal
DPP-IV inhibitors: Inhibit degradation of natural GLP-1
Glitazones: Enhance glucose transport into cells
Insulin
LIVER
Stimulates glycogen formation from glucose
beta cell
PANCREAS
alpha cell
GLP-1 Increases insulin production, inhibits glucagon release
Glycogen
Glucose
Stimulates glycogen breakdown and conversion of fats and proteins to glucose
Glucagon
Low blood glucose - between meals
GLP-1 analogues: Mimic effects of natural GLP-1
Biguanides: Inhibit glycogen breakdown
Insulin causes blood glucose to fall
Negative feedback mechanism keeps tight regulatory control over blood glucose concentration

Source: Rang, Dale & Ritter, Deutsche Bank

Pharmacological treatment

Diabetes is not yet curable, but it can be well treated. The goals of diabetes management are to attain and maintain a near-normal blood sugar level and reduce the risk of complications. In Type 1 diabetes, treatment will depend on the individual's needs, but typically consists of an insulin regimen, which at present requires the regular injection of differing formulations of insulin. This will often comprise daily injections of long-lasting insulin to provide a basal level similar to that of the normal body, together with separate injections of rapid/intermediate acting product to provide a 'top-up' at meal times.

For Type 2 diabetics who have become insensitive to their own insulin, treatment initially focuses on diet and exercise so that lower amounts of effective insulin can control blood sugar adequately. Failing this, a range of oral drug regimens may be implemented. Medication is designed to address the three basic abnormalities that contribute to the development of hyperglycaemia, namely peripheral insulin resistance, excessive liver glucose production and impaired insulin secretion.

Oral medications

At present, there are five main classes of oral medication available, the main features of which are highlighted in Figure 108.

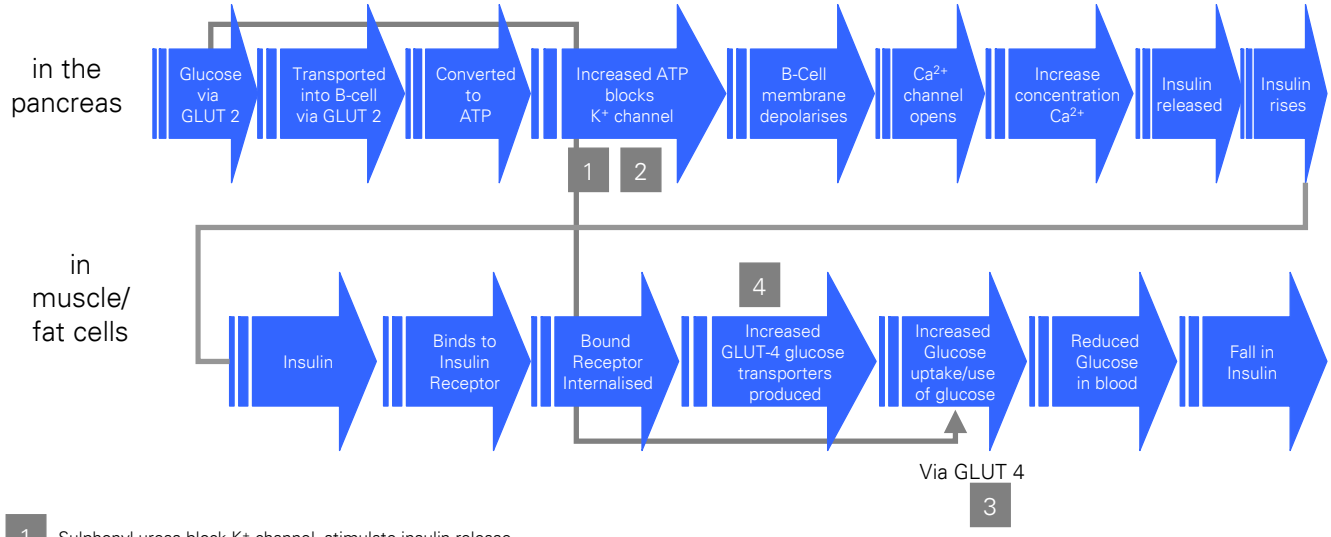
Figure 108: The main classes of drugs for control of blood glucose

Drug class	Sulphonylureas	Biguanides	Glitazones	Secretagogues	Alpha-glucosidase inhibitors
Sales 2004	$1.0bn	$0.7bn	$3.9bn	$0.5bn	$0.9bn
Dose per day	One-three	Two-three	One-two	Per meal	Three
Insulin levels	Increase	Decrease	Decrease	Increase	n/a
Risk of hypoglycaemia	High	Low	Low	Low	Low
Increased body weight	Yes	No	No	No	No
Reduction in lipids	No	Yes	Yes	No	No

Source: Company data, Deutsche Bank estimates

- **Sulphonylureas**: First developed in the 1950s, the sulphonylureas account for over 50% of the oral diabetes market by volume but because they are largely generic, only 15% of the market by value. They work by stimulating the beta cells to increase insulin production rather than by re-sensitising the body to insulin. They may, however, cause hypoglycaemia (low blood sugar), which can result in coma or death if insufficient carbohydrates are ingested. In addition, by causing constant stimulation of the beta cells, they may lead to the eventual 'burn-out' of these cells. The leading sulphonylureas by value include Glucotrol, and Amaryl.
- **Biguanides**: These are oral hypoglycaemic agents that do not require functioning beta cells. They act by suppressing the breakdown of glycogen in the liver and enhancing glucose uptake in skeletal muscle (re-sensitising). Their predominant advantage over the sulphonylureas is that they do not cause hypoglycaemia. Side effects can include stomach upset and, in rare cases, lactic acidosis. The lead product in this class is Bristol-Myers Squibb's Glucophage (metformin), which is now available generically.
- **Rapid-acting insulin secretagogues**: These are a relatively new class of compound to be taken at mealtimes. As with the sulphonylureas, they stimulate beta cells to produce insulin. However, both onset and offset of insulin production is more rapid, thereby more accurately replicating the body's own insulin profile, an advantage over the sulphonylureas. At present, are only two marketed secretagogues, Novo's Prandin/NovoNorm and Novartis' Starlix.
- **Alpha glucosidase inhibitors**: A small class of drugs that works by reducing the absorption of carbohydrates in the small intestine, and therefore, the level of glucose in the blood. Side effects include flatulence, diarrhoea and abdominal pain. The lead product in this class is Bayer's Glucobay/Precose.
- **Glitazones**: Also known as peroxisome proliferator-activated gamma receptor agonists (PPARs), these represent a new class of compounds that act as true insulin sensitisers. They act by stimulating the transport of glucose into the cell (via GLUT-4 glucose transport proteins) and by increasing the lipid metabolism activity of peroxisomes. The result is an increase in the internalisation of glucose following the release of insulin. Some incidence of heart murmur has been evident as a side effect. There are currently two key marketed glitazones namely, Actos (Eli Lilly/Takeda) and Avandia (GlaxoSmithKline). In addition, several broader-acting PPAR agonists are currently in late-stage clinical development. However, following evidence of tumours seen in rodents, the FDA issued new guidance in mid-2004 requiring all new PPAR agonists to complete two-year rodent safety studies before initiating any trials in humans of longer than six months.

Figure 109: Pathways for insulin release and activation



1 Sulphonyl ureas block K+ channel, stimulate insulin release

2 Insulin Secretagogues transiently block K+ channel, stimulate insulin release

3 Biguanides aid glucose uptake in GLUT 4

4 Glitazones act on peroxisome, proliferation activated receptor to stimulate GLUT 4 production and glucose transport

Source: Rang, Dale & Ritter

Figure 110: Leading drugs for use in type II diabetics

Brand name	Generic name	Producer	Class	Sales 2004
Glucotrol	glipizide	Pfizer	Sulphonylurea	$0.1bn
Amaryl	glimepride	Sanofi-Aventis	Sulphonylurea	$0.8bn
Glucophage	metformin	Bristol-Myers Squibb	Biguanide	<$0.1bn
Prandin/NovoNorm	repaglinide	Novo Nordisk	Secretagogue	$0.3bn
Starlix	nateglinide	Novartis	Secretagogue	$0.2bn
Avandia*	rosiglitazone	GlaxoSmithKline	Glitazone	$2.0bn
Actos	pioglitazone	Eli Lilly/Takeda	Glitazone	$1.7bn
Glucobay/Precose	acarbose	Bayer	Alpha glucosidase inhibitor	$0.3bn
Basen	voglibose	Takeda	Alpha glucosidase inhibitor	$0.5bn

*Source: Company data, Deutsche Bank estimates *Includes Avandamet (rosiglitazone + metformin)*

Insulin

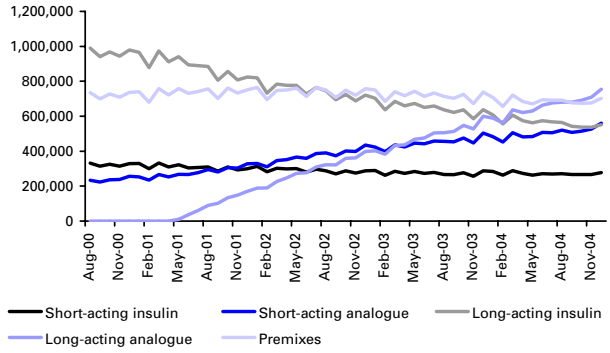
In the case of Type 1 patients and in around a third of Type 2 patients, insulin becomes the mainstay of therapy. In 2004, the world market for insulin was worth approximately $6.5bn, shared among three participants, Novo Nordisk (48%), Eli Lilly (33%) and Sanofi-Aventis (19%). This market is primarily broken down into three key types of insulin:

- **Short-acting insulin:** Conventional short-acting insulins, including Lilly's Humalin R and Novo's Novalin R, are short-acting formulations that must be taken before mealtimes to provide a temporary increase in insulin levels. More recently, Lilly and Novo have introduced short-acting analogues, namely, Humalog and Novolog, which provide a more immediate onset of action.
- **Long-acting (NPH or basal) insulin:** Humulin N and Novalin N are long-acting insulin formulations with a duration of action of approximately 16-18 hours, thus requiring twice daily dosing in many patients. Because they provide a steady level of background insulin but no mealtime peaks, they are usually taken in combination with a short-acting insulin or short-acting analogue. Sanofi-Aventis' Lantus, launched in 2000, is the first long-acting

insulin analogue. Lasting a full 24 hours, it is the only product requiring true once daily dosing. Novo Nordisk has also developed a basal insulin analogue, Levemir, which was launched in Europe in 2004 and should be launched in the US in 2006 pending approval of Novo's manufacturing facilities. However, in contrast to Lantus, Levemir is indicated for use once- or twice-daily.

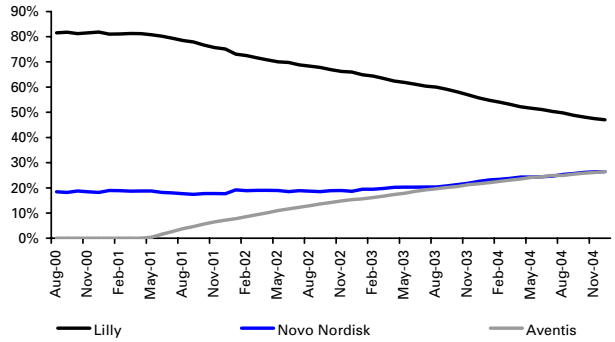
- **Premixes:** Premixes, such as Humalin 70/30 and Novolin 70/30, are combinations of short- and long-acting insulins. (Lilly's Humalog 75/25 is a premix incorporating a short-acing analogue as is Novo's NovoMix.) They are administered several times daily and provide the benefits of both short-acting and basal insulin. While not as effective as separate administration of a short-acting and a long-acting formulation, they have gained popularity due to more convenient dosing.

Figure 111: US insulin market (TRX) by type



Source: IMS Health

Figure 112: US insulin market share by company



Source: IMS Health

Clinical end-points

The main objective of Type II diabetes treatment is the controlled reduction of blood glucose levels. This is measured by glycosylated haemoglobin (HbA1c) levels, which represent the amount of glucose in the blood stream. In non-diabetics, HbA1c levels are typically below 6%, whereas in diabetics, they are typically over 8%. Current ADA (American Diabetes Association) guidelines recommend that HbA1c levels should be below 7%.

Pipeline products

A number of 'dual' PPAR agonists are currently in late-stage development or registration. These drugs act upon the PPAR-gamma receptor, which is associated with increased insulin sensitivity and reduced glucose levels, as well as the PPAR-alpha receptor, which is associated with reduced triglycerides and increased HDL cholesterol. The most advanced of these is Bristol-Myer's muraglitazar, which was submitted to the FDA in late 2004 and will be co-marketed by Merck.

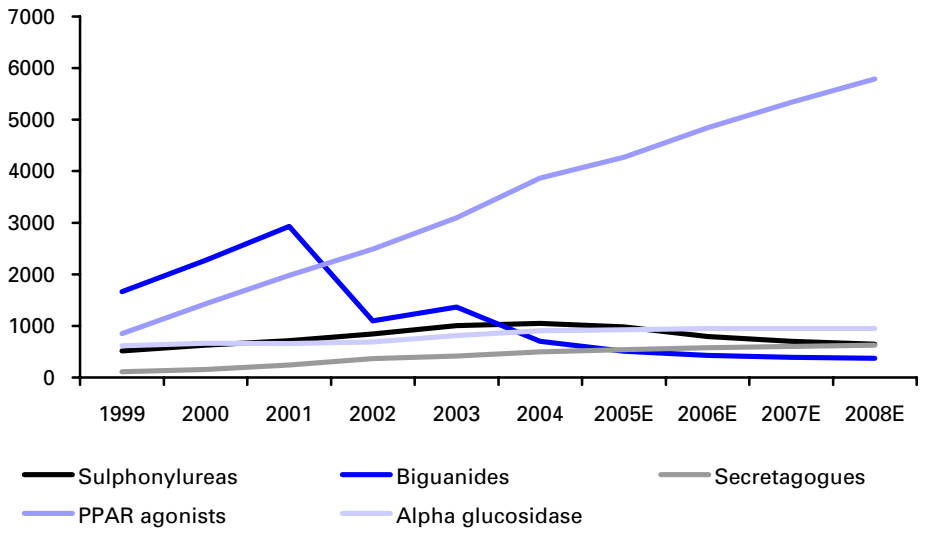
Elsewhere, a number of companies are focused on the glucagon-like peptide 1 (GLP-1) pathway which is responsible for increasing insulin production and inhibiting glucagon release. Lilly and partner Amylin recently received FDA approval for exenatide which is designed to mimic the effects of GLP-1. Separately, Merck and Novartis are developing dipeptidyl peptidase 4 (DPP-4) inhibitors, which aim to inhibit GLP-1 degradation by the enzyme DPP-4. Both drugs are currently in Phase III with filing expected in 2006. However, given that inhibition of the closely related DPP-8 and DPP-9 proteins is associated with fatal toxicities in rodents, we expect the drugs' relative selectivity for DPP-4 will be critical and the safety of this class will be scrutinised.

Figure 113: Selected late-stage pipeline products for diabetes

Name	Sponsor	Class/Mechanism	Status	Est filing
Byetta (exenatide)	Amylin/Lilly	GLP-1 analogue	Launch 2005	Approved
Apidra	Sanofi-Aventis	Short-acting insulin analogue	Launch 2006	Approved
Levemir	Novo Nordisk	Long-acting insulin analogue	Launch 2006	Approved
Exubera	Pfizer/Sanofi-Aventis/Nektar	Inhaled insulin	Launch 2006	Filed
Pargluva (muraglitazar)	BMS/Merck	PPAR alpha/gamma agonist	Launch 2007*	Filed
MK-431	Merck	DPP-4 inhibitor	Phase III	2006
LAF 237	Novartis	DPP-4 inhibitor	Phase III	2006
Galida	AstraZeneca	PPAR alpha/gamma agonist	Phase III	2007
liraglutide	Novo Nordisk	GLP-1 analogue	Phase II	2007
inhaled insulin	Lilly/Alkermes	Inhaled insulin	Phase II	>2007
NN1998 (AERx)	Novo Nordisk/Aradigm	Inhaled insulin	Phase II	>2007

*Source: Deutsche Bank, Company information *Filed late 2004 but protracted regulatory review expected to delay approval to 2007.*

Figure 114: Sales revenues for oral diabetes drugs ($m)



Source: Wood Mackenzie

Figure 115: Sales revenues for oral diabetes drugs ($m)

	1999	2000	2001	2002	2003	2004	2005E	2006E	2007E	2008E
Sulphonylureas	515	627	711	842	1004	1050	982	794	700	646
Biguanides	1661	2269	2927	1096	1363	704	508	425	390	370
Secretagogues	114	153	244	364	415	497	542	576	602	624
PPAR agonists	853	1427	1981	2490	3094	3868	4271	4841	5338	5790
Alpha glucosidase	612	662	656	689	812	904	923	948	949	949

Source: Wood Mackenzies

Atherosclerosis

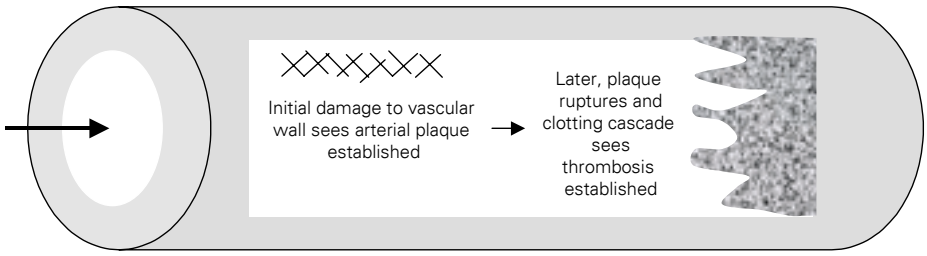
Atherosclerosis is a disease of the large and medium-sized arteries. It evolves over many decades, during most of which time it is clinically silent. It arises as a consequence of damage to the arterial wall, although quite how this initial damage is caused is still unclear. Among other theories, it has been postulated that the damage may arise from some form of bacterial infection or as a consequence of turbulence in the blood stream as a result of hypertension.

Also known as hardening of the arteries, atherosclerosis involves the creation of a plaque consisting of cholesterol, white blood cells, platelets and fibrin on the damaged area of the artery. Although the plaque in itself is not dangerous, if it ruptures, it exposes subendothelial (beneath the inner lining of the arteries) material that acts as a focus for thrombosis (blood clotting). Consequently, it is the major cause of ischaemic heart disease (that is, lack of blood to the muscles of the heart) and as such is the leading cause of death in the industrialised world. Numerous risk factors exist including cigarette smoking, hypertension, obesity, lack of physical activity and increased plasma concentrations of certain cholesterols (namely LDL-cholesterol). Some families may also have a genetic predisposition.

Although the exact cause of damage to the arterial wall is not yet fully understood, the pathogenesis of plaque creation is becoming clearer. Explained crudely, the injury to the lining of the arteries (endothelium) encourages white blood cells and low density lipoproteins (LDL-cholesterol) to attach to the damaged area. Rather than being released, as is the case in healthy endothelium, the LDL-cholesterol is oxidised and hardens, after which it is absorbed by specialised white blood cells called macrophages. These necrotic macrophages then migrate under the endothelium, after which the damaged area is covered by a fibrous cap of platelets, fibrin and regenerated smooth muscle. It is this fibrous mesh overlying a core of lipid and necrotic (dead) tissue that is called a plaque and that forms the substrate on which thrombosis can develop if the plaque ruptures.

Clearly, several steps in the atherogenic process are potential targets for pharmacological attack, not least the synthesis and breakdown of LDL-cholesterol. Equally, the perceived importance of hypertension as a potential cause of initial endothelial damage makes it an important area for pharmacological investigation. Both of these strategies are discussed over the following pages.

Figure 116: Stages in atherosclerosis


Initial damage to vascular wall sees arterial plaque established
Later, plaque ruptures and clotting cascade sees thrombosis established

Source: Deutsche Bank

NOTES

Hypertension

- Worldwide market for anti-hypertensives in 2004 worth about $25bn
- Key classes include beta blockers, ACE inhibitors, calcium antagonists and the angiotensin II inhibitors (ARBS)
- Five-year growth of 3% supported by uptake of ARBs but offset by generic erosion in other classes
- Lead products: Diovan (Novartis ARB), Norvasc (Pfizer calcium antagonist)

Hypertension, or high blood pressure, is a common disorder that greatly increases the likelihood of heart attack, stroke and renal failure if not effectively treated. Until the 1950s, there was no effective treatment. However, today there are several classes of drug that can be used to treat the disease effectively. Hypertension affects roughly one in four North American adults. In 90-95% of cases, the cause of the increase in blood pressure is not known, although 60% of those suffering are overweight.

Physiology

Blood pressure in the arteries is generated by the interplay between blood flow and resistance to blood flow. It reaches a peak during the pumping of the heart (cardiac systole) and a trough at the end of the heart's period of relaxation (diastole). In effect, it can be defined as the product of cardiac output (CO) and the total peripheral resistance (TPR) offered by the blood or vascular system. Cardiac output, which is a function of heart rate, stroke volume and the capacity of blood in the veins, is the major determinant of systolic pressure, while peripheral resistance largely determines diastolic pressure. As such, treatment is typically directed at altering these variables.

Arterial blood pressure is measured in millimetres of mercury and recorded as systolic pressure over diastolic. Hypertension is defined as a level of systolic blood pressure or SBP (blood pressure during the contraction phase of the heartbeat) of 140mm Hg or above, or a level of diastolic blood pressure or DBP (pressure during the resting stage of the heart) of 90mmHg or above. This compares with normal blood pressure of 120mmHg or below for SBP and 80mm Hg or below for DBP.

Several biological systems control blood pressure and a sophisticated feedback system exists. Key regulatory mechanisms, each of which is mentioned below, include the actions of the nervous system, hormones, control of body fluid and regulators produced by the blood vessels themselves.

- **Nervous system:** One of the key mechanisms for maintaining blood pressure is through the actions of the nervous system. Noradrenalin, a chemical messenger, is released by nerve endings located on blood vessels (including those of the heart) and acts on alpha and beta receptors. Stimulation of alpha receptors on veins and arteries serves to narrow the vessels (called vasoconstriction), thereby increasing peripheral resistance and, consequently, blood pressure. Equally, stimulation of beta receptors in the heart ('beta 1' receptors) results in an increase in contractility and heart rate, thereby also increasing blood pressure (note most beta blockers act on this beta 1 receptor). Countering this, a system of pressure sensors or baroreceptors located at the nerve endings that attach to large arteries (including those of the heart) provide feedback to the brain, and hence, the central nervous system, so impacting the rate of noradrenalin release.

- **Hormones:** Through both its actions on the vascular system and its role in controlling the excretion of sodium, the so-called renin-angiotensin system is one of the most important mechanisms for control of blood pressure. It is also the key pathway at which two major classes of drugs are directed, namely the angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs). Produced by the kidneys, renin acts on a blood protein called angiotensinogen, converting it to angiotensin I. This is then converted by the angiotensin converting enzyme to angiotensin II, which has three key properties that increase blood pressure. These include:
  - powerful vasoconstriction, so increasing peripheral resistance;
  - increased release of noradrenaline from nerve terminals, so reinforcing vasoconstriction and the rate and force of heart contraction; and
  - secretion of aldosterone, a hormone that facilitates sodium retention by the kidneys and, consequently, water retention.
- **Vascular regulators.** The lining of blood vessels also has an important part to play in hypertension. Among other actions, endothelial cells produce nitric oxide, which acts as a vasodilator. The presence of calcium channels also regulates the concentration of calcium within blood vessel muscle and hence constriction/dilation (calcium ions stimulate muscle activity). It is on these calcium channels in both the heart and the peripheral blood system that the calcium antagonists have their effect.
- **Control of body fluid:** Blood pressure can also be controlled by reducing the total amount of fluid in the blood vessels. Regulated by the kidneys, water retention is influenced by the concentration of sodium in the blood. Diuretics act to increase the excretion of water and reduce blood pressure.

Pharmacological treatment

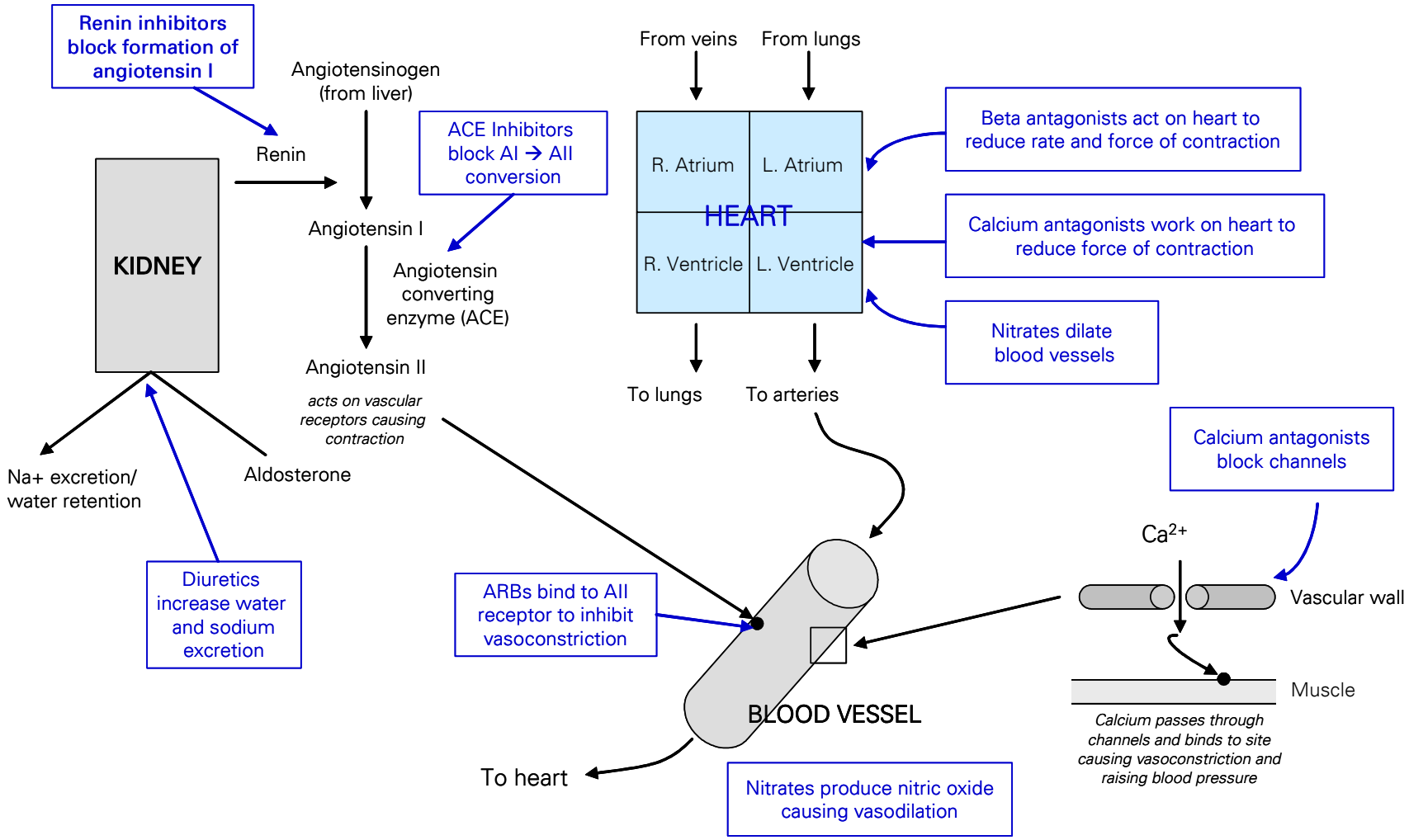
A large number of drugs are used to treat hypertension. The market, however, is dominated by four main classes. These are the beta-blockers, calcium antagonists, ACE inhibitors and ARBs. Although each of these classes is indicated as a monotherapy, combination regimens (which often include a diuretic) have become the mainstay of hypertension therapy. Each of these key classes are described in the figures below.

Figure 117: Summarised features of the leading classes of hypertensive agents

Class	Beta blockers	Ca2+ antagonists	ACE inhibitors	ARBS
Sales 2004	$4.6bn	$7.9bn	$6.4bn	$11.6bn
Lead product	Toprol	Norvasc	Delix/Tritace/Altace	Diovan
Main action on	Heart	Heart/vascular	Vascular	Vascular
Side effects	Bronchospasm, CHF, lower HDL	Swelling	Cough, swelling	Swelling

Source: Deutsche Bank

Figure 118: The renin-angiotensin system and its effect on blood pressure



Source: Deutsche Bank

Beta blockers: The discovery of beta blockers in the 1960s represented a major breakthrough in cardiac therapy. The oldest of the four lead classes of anti-hypertensives, beta blockers act predominantly on the heart. They work by inhibiting the stimulation of the beta adrenergic receptor in the heart, thereby slowing the rate and strength of contraction. This reduces cardiac output and, with it, blood pressure.

Figure 119: Leading beta blockers

Name	Generic name	Producer	2004 sales
Toprol XL/Seloken	metoprolol	AstraZeneca	$1.4bn
Tenormin	atenolol	AstraZeneca	$0.4bn
Coreg	carvedilol	GlaxoSmithKline	$0.8bn

Source: Company data

Calcium antagonists: Calcium is vital for muscle contraction. An increase in the concentration of calcium within muscle cells precipitates their contraction. In essence, calcium antagonists work by preventing the inflow of calcium through calcium channels on heart and vascular tissue. This reduces both the strength of the heart's contraction and reduces vascular constriction. As such, the product can also be used for angina. Patent expiry on several key products, not least Adalat, Cardizem and Procardia, has led to a decline in class sales.

Figure 120: Leading calcium antagonists

Name	Generic name	Producer	2004 sales
Norvasc	amlodipine	Pfizer	$4.5bn
Adalat	nifedipine	Bayer	$0.8bn
Plendil	felodipine	AstraZeneca	$0.5bn

Source: Company data

Angiotensin converting enzyme (ACE) inhibitors: ACE inhibitors are one of the two classes of drugs that work on the renin-angiotensin system. They work by preventing the creation of angiotensin II, a powerful vasoconstrictor. With generic competition for many of the leading compounds (Vasotec, Prinivil, Zestril and most recently, Accupril) arriving in the last few years, class sales have come under significant pressure.

Figure 121: Leading ACE inhibitors*

Name	Generic name	Producer	2004 sales
Vasotec	enalapril	Merck	$0.7bn
Zestril	lisinopril	AstraZeneca	$0.4bn
Delix/Tritace/Altace	ramipril	Sanofi-Aventis/King	$1.7bn
Prinivil	lisinopril	Merck	<$0.1bn
Accupril	quinapril	Pfizer	$0.7bn
Lotensin	captopril	Novartis	$0.2bn

Source: Company data **Includes fixed-dose ACE-diuretic combinations*

Angiotensin II receptor antagonists (ARBs): The newest class of hypertensive treatments, the angiotensin II inhibitors, also act on the renin-angiotensin system but do not cause the dry cough that has proved an irritating side effect of the ACE inhibitor class. To date, they are only used as first-line therapy in roughly 10% of patients but their utilisation continues to rise.

Figure 122: Leading angiotensin II inhibitors*

Name	Generic name	Producer	2004 sales
Cozaar	losartan	Merck	$2.8bn
Diovan	valsartan	Novartis	$3.1bn
Avapro	irbesartan	Sanofi-Aventis/BMS	$1.8bn
Atacand/Blopress	candesartan	AstraZeneca/Takeda	$1.7bn
Benicar	olmesartan	Sankyo/Forest	$0.4bn

*Source: Company data *Includes fixed-dose ARB-diuretic combinations.*

Clinical end-points

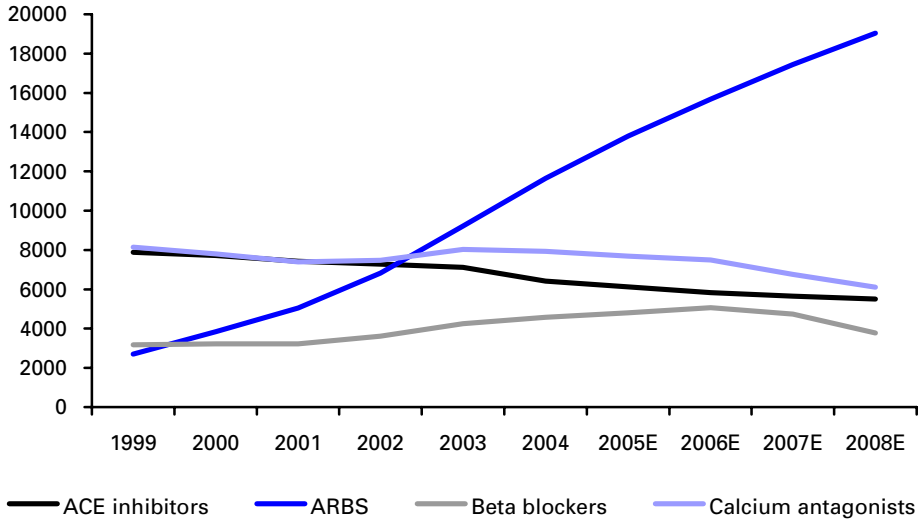
The key clinical end-points for hypertension drugs are their impact on both systolic (upper) and diastolic (lower) blood pressure. Since the objective of therapy is to lower blood pressure, the greater the reduction, the more effective and interesting the product. Side effects must, of course, also be considered.

Pipeline products

Despite the fact that roughly 70% of hypertension patients are not treated to goal blood pressure levels and there still remains a large unmet medical need, there has been limited successful advancement in this field since the introduction of the ARBs in the mid-1990s. Much attention has focused on a class of drug known as neuro-endopeptidase (NEP) inhibitors. The so-called ACE-NEP inhibitors act on the renin-angiotensin system but also prevent the degradation of a cardio-protective hormone, so helping the heart muscle to relax. While the most advanced of these, Bristol-Myers' Vanlev, was shown to be more effective at reducing both diastolic and systolic pressure than existing hypertension drugs, safety concerns, including incidence of angioedema (swelling around the throat), led to Vanlev's ultimate demise. Although other companies continue to pursue research in this area, none of these projects, including molecules at Lilly and GSK, have as yet managed to advance past early stage clinical trials.

The other class attracting increased interest is that of renin inhibitors. Novartis' SPP100 (aliskerin) is the most advanced compound in this class, while companies such as Merck and Actelion have preclinical stage programmes ongoing. By binding to renin, SPP100 acts upon the very beginning of the renin-angiotensin cascade, inhibiting the conversion of angiotensinogen to angiotensin I. Although the ACEs and ARBs act upon downstream steps in the same renin-angiotensin system, the rationale for the direct renin inhibitors is that the ACEs and ARBs tend to produce a rise in plasma renin levels via a negative feedback loop, thereby making their task that much harder. However, while direct renin inhibition suggests the potential for greater efficacy, development of the class has been plagued by issues of low bioavailability. Novartis' SPP100 is currently being evaluated in Phase III trials as a monotherapy and in combination with Diovan. However, published data to date on SPP100 have demonstrated only modest efficacy, suggesting that the drug will be relegated to third- or fourth-line therapy and thus do little to alter the current treatment paradigm.

Figure 123: Sales revenues for hypertension drugs ($m)



Source: Wood Mackenzie

Figure 124: Sales revenues for hypertension drugs ($m)

	1999	2000	2001	2002	2003	2004	2005E	2006E	2007E	2008E
ACE inhibitors	7888	7720	7426	7281	7123	6412	6125	5825	5646	5508
ARBS	2709	3840	5043	6817	9216	11649	13795	15677	17436	19044
Beta blockers	3175	3229	3232	3609	4251	4577	4800	5058	4734	3770
Calcium antagonists	8137	7795	7389	7471	8024	7936	7689	7497	6754	6105

Source: Wood Mackenzie

Dyslipidaemia

- Worldwide cholesterol-lowering market in 2004 was worth roughly $22.7bn
- Forecast five-year compound annual growth of 8%, boosted by increased marketing noise surrounding new product launches
- Class leaders are Pfizer's Lipitor and Merck's Zocor

Cholesterol is a waxy substance that occurs naturally in the body. However, the amount required by the body is relatively small and excess arising from diet may be deposited on the arteries. As described earlier, this can result in the coronary arteries becoming clogged and may lead to chest pain (angina) or, should an artery in the heart become completely blocked, tissue in the heart 'dies' producing a heart attack (myocardial infarction). Clinical studies have shown that a 1% increase in certain cholesterol levels (LDL-C or 'bad' cholesterol) is associated with a 2% increase in the risk of coronary heart disease. In patients without coronary heart disease, desirable levels of total cholesterol are stated as being under 200mg/dL, of which LDL-cholesterol should be under 130mg/dL.

Physiology

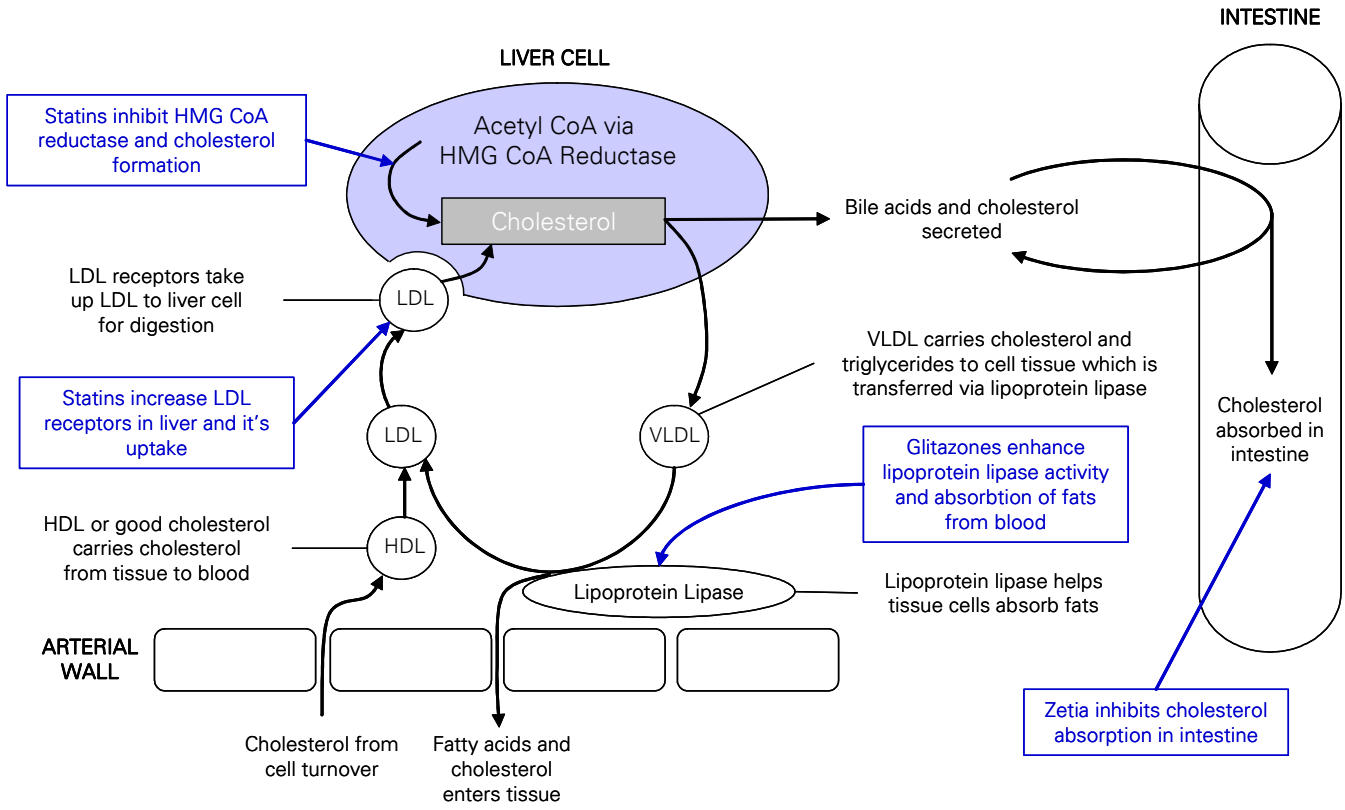
Cholesterol is vital for normal body function. It is a core component of cell membranes and is the key building block for many internally produced hormones. It also forms an important part of the bile acids that are secreted by the liver into the gastrointestinal tract to aid digestion. While much of the cholesterol that we need is absorbed through the gut wall from our food, cholesterol is also produced internally by the liver. The rate-limiting step in its production in the liver relies on an enzyme called HMG-CoA reductase (3-hydroxy 3-methylglutaryl-CoA).

Because cholesterol itself is unable to pass through cell walls, it is transported about the body in a complex called a lipoprotein. As well as cholesterol, lipoproteins consist of triglycerides, phospholipids and proteins called apolipoproteins. There are several different classes of lipoproteins, each of which plays a different role and which are differentiated from each other by size, density and the relative proportions of core lipids that they carry. Key among these are very low density lipoproteins (VLDL), low density lipoproteins or (LDL) and high density lipoproteins (HDL). The function of each is as follows:

- **VLDL** - These lipoprotein complexes carry triglycerides (fats) and cholesterol from the liver to the tissue, wherein triglycerides are removed and pass into tissue cells with the help of an enzyme called lipoprotein lipase. Triglycerides provide a source of energy.
- **LDL** - Put crudely, after VLDL loses its triglyceride, it becomes cholesterol rich and is called LDL. Some of the LDL cholesterol is also taken up by the tissues. Much, however, returns to the liver, where it is ingested via specific LDL receptors.
- **HDL** - This type of lipoprotein absorbs cholesterol derived from cell breakdown in tissues and carries it back into the blood stream, wherein it is transferred to LDL.

It is cholesterol-rich LDL that is the key protagonist of atherosclerosis, hence, its title of 'bad cholesterol'. By contrast, as a carrier of cholesterol away from tissue, HDL cholesterol is often referred to as 'good cholesterol'.

Figure 125: The statins inhibit HMG-CoA reductase


INTESTINE
LIVER CELL
Statins inhibit HMG CoA reductase and cholesterol formation
Acetyl CoA via HMG CoA Reductase
Cholesterol
Bile acids and cholesterol secreted
LDL receptors take up LDL to liver cell for digestion
LDL
VLDL carries cholesterol and triglycerides to cell tissue which is transferred via lipoprotein lipase
Statins increase LDL receptors in liver and it's uptake
LDL
VLDL
Cholesterol absorbed in intestine
Glitazones enhance lipoprotein lipase activity and absorbtion of fats from blood
HDL or good cholesterol carries cholesterol from tissue to blood
HDL
Lipoprotein Lipase
Lipoprotein lipase helps tissue cells absorb fats
ARTERIAL WALL
Zetia inhibits cholesterol absorption in intestine
Cholesterol from cell turnover
Fatty acids and cholesterol enters tissue

Source: Rang, Dale & Ritter

Pharmacological treatment

Several drugs are used to treat raised levels of cholesterol. Of these, by far the largest and most important are the statins. Introduced in 1987, the statin class today realises annual sales of over $21bn globally and continues to grow at healthy high single-digit rates. Clinical trials have shown that by reducing the level of LDL cholesterol in the blood by up to 60%, as well as modestly increasing levels of HDL, mortality by heart attack or stroke can be reduced by around a third. The class is generally well tolerated, with mild and infrequent side effects, such as stomach upset, insomnia and rash.

The statins have a two-fold effect on cholesterol, each of which is illustrated above. Not only are they potent inhibitors of HMG-CoA reductase, so limiting the production of cholesterol in the liver, but also by reducing internal production of cholesterol, the statins stimulate the synthesis of LDL receptors and so increase the clearance of cholesterol from blood plasma.

Today, there are several statins available on the market. The class leader is Pfizer's Lipitor (atorvastatin), which, at its maximum dose of 80mg, has been shown to reduce the level of LDL cholesterol in the plasma by around 60%. Since its launch in 1997, Lipitor has rapidly gained market share, becoming the world's first $10bn drug in 2004.

The statin market took a hit in August 2001 with the recall of Baycol, which was expected to earn approximately $900m, or 15% of Bayer's 2001 pharmaceutical sales, prior to the withdrawal. The recall followed a number of cases of rhabdomyolysis (muscle wasting), primarily in patients taking the highest 80 mg dose and who were concurrently taking the fibrate gemfibrozil. Amid concerns over a possible class effect, the newest entrant, AstraZeneca's Crestor, faced a rigorous FDA review. However, despite the FDA's

endorsement and an increasing patient database substantiating its statin-like profile, the drug has continued to suffer from negative noise regarding safety concerns.

Aside from the statin class, Merck and Schering-Plough recently launched Zetia (ezetimibe), the first in a new family of cholesterol-lowering drugs that inhibit the absorption of cholesterol in the intestine. This distinct mechanism of action makes Zetia complementary to the statins, which work in the liver. In clinical trials, Zetia demonstrated a 25% further reduction in LDL, along with improvements in both HDL and triglyceride levels, when added to ongoing statin therapy. Given that the majority of Zetia prescriptions are used in combination with statins, Merck and Schering-Plough followed up the Zetia launch with a Zetia-Zocor fixed combination called Vytorin. This drug has been positioned as potent first-line alternative to the likes of Lipitor and Crestor.

Figure 126: Comparison of cholesterol-lowering properties of leading statins

Product (max dose)	Total cholesterol	LDL	HDL	Triglycerides
Lipitor (80mg)	-45%	-60%	+5%	-37%
Zocor (80 mg)	-31%	-36%	+16%	-33%
Pravachol (80 mg)	-27%	-37%	+3%	-19%
Lescol (80 mg)	-27%	-36%	+6%	-18%
Crestor (40 mg)	-46%	-63%	+10%	-28%
Vytorin (10mg/80mg)	-43%	-60%	+6%	-31%

Source: Company data

Figure 127: Leading cholesterol-lowering drugs

Brand	Generic	Producer	2004 sales
Lipitor	atorvastatin	Pfizer	$10.8bn
Zocor	simvastatin	Merck	$5.2bn
Pravachol	pravastatin	BMS	$2.6bn
Lescol	fluvastatin	Novartis	$0.8bn
Mevalotin	pravastatin	Sankyo	$0.9bn
Crestor	rosuvastatin	AstraZeneca	$0.9bn
Zetia	ezetimibe	Schering-Plough/Merck	$1.1bn
Vytorin	ezetimibe/simvastatin	Schering-Plough/Merck	$0.1bn

Source: Company data

Clinical end-points

The key clinical end-point for the statins is their efficacy in reducing total blood cholesterol over a defined period (typically eight weeks). Within this, data should measure the reduction in LDL-C, increases in HDL-C and reduction in triglycerides. Following the Baycol incident, increased emphasis is also being placed on a clean safety profile.

Pipeline products

With Lipitor, Crestor and Vytorin already offering potent (>60%) LDL cholesterol lowering, attention has turned to drugs that more specifically target HDL cholesterol. In particular, Pfizer and Roche are developing novel drugs that inhibit the cholesteryl ester transfer protein (CETP), which is responsible for transferring cholesterol away from good HDL to another lipoprotein called apolipoprotein-B. In Phase II studies, Pfizer's torcetrapib (120mg once daily) was shown to raise HDL by 46%, while Roche/Japan Tobacco's JTT-705 (900mg once daily) increased HDL by 34%. However, in light of the immense volume of data emphasising the cardiovascular benefit of lowering LDL (and the lesser data available supporting the independent benefits of raising HDL), Pfizer is developing torcetrapib as a combination product with its market leading statin Lipitor. Similarly, Roche plans to combine JTT-705 with

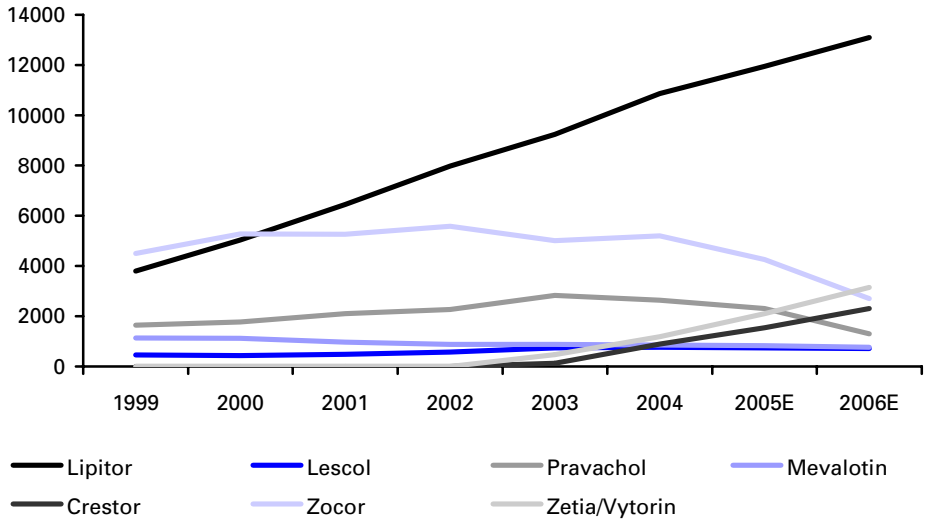
a generic statin (most likely simvastatin, we believe). Importantly, the approval timeline and requirements for these drugs remain uncertain. In particular, while Pfizer hopes to file its torcetrapib/Lipitor combination in 2007 on the basis of imaging studies which look at atherosclerotic regression, it is unclear whether the FDA will accept these data, or if it will require the results of morbidity/mortality outcome studies which will only become available in early 2010.

Figure 128: Selected pipeline drugs for dyslipidaemia

Name	Sponsor	Class/Mechanism	Status	Est filing
Livalo	Sankyo	Statin	Phase II	2007
CS-505	Sankyo	ACAT inhibitor	Phase II/III	2007
Lipitor-torcetrapib	Pfizer	Statin + CETP inhibitor	Phase III	2007
JTT-705	Roche/Japan Tobacco	CETP inhibitor	Phase II	>2007

Source: Deutsche Bank

Figure 129: Growth forecasts for the leading cholesterol lowering drugs ($ m)



Source: Company data, Deutsche Bank estimates

Figure 130: Growth forecasts for the leading cholesterol lowering drugs ($ m)

		1999	2000	2001	2002	2003	2004	2005E	2006E
Lipitor	Pfizer	3796	5029	6449	7972	9231	10862	11950	13100
Lescol	Novartis	458	429	482	577	734	758	745	709
Pravachol	Bristol-Myers Squibb	1637	1766	2101	2266	2827	2635	2300	1300
Mevalotin	Sankyo	1133	1126	972	884	878	849	830	766
Crestor	AstraZeneca	0	0	0	0	129	894	1536	2303
Zocor	Merck & Co	4495	5280	5260	5580	5012	5196	4250	2700
Zetia/Vytorin	Schering-Plough/Merck	0	0	0	0	471	1189	2100	3150

Source: Deutsche Bank

Thrombosis and the Antithrombotics

- World anti-thrombotic market valued at around $12bn in 2004
- 12% five-year growth forecast, driven by heparins and anti-platelets
- Lead products include Sanofi-Aventis' Lovenox, a low molecular weight heparin, and Plavix, an anti-platelet agent co-marketed with BMS

Thrombosis is the formation of a blood clot in the blood system (or vasculature) in the absence of bleeding. In the arteries, it tends to arise following the rupture of an atherosclerotic plaque, while in the veins, it is generally associated with static blood flow. Once a thrombus is established, it can block key blood vessels, including those in the heart, or it can break away forming an embolus, which may later lodge in the lungs (pulmonary embolism) or the brain (cerebral embolism), causing a stroke.

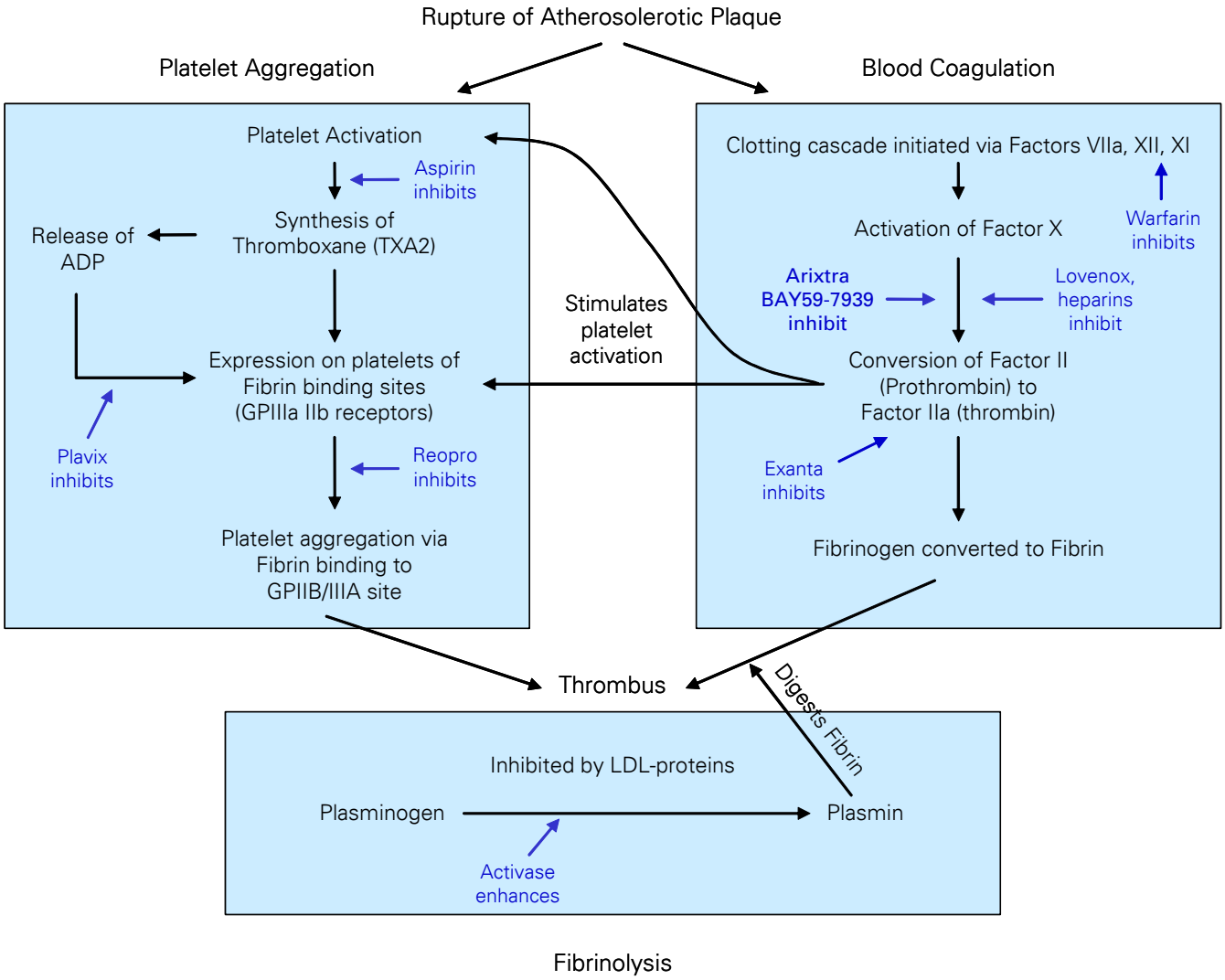
Physiology

Despite the absence of bleeding, the creation of a thrombus involves the initiation of the blood-clotting cascade. In healthy vascular tissue, the arterial lining (called the endothelium) produces proteins that keep the clotting cascade in check. However, in tissue covered by a plaque, these proteins are not produced and the plaque represents a substrate on which a thrombus can grow. Key to this is the activation of platelets and a host of other blood proteins, such as fibrinogen, thrombin and other blood enzymes, or 'factors', which travel about the body in the blood system in an inactive state. Once activated, the various factors form part of a huge chain-reaction that serves to amplify the clotting cascade.

The creation of a thrombus can simplistically be broken down into three different chains, each of which inter-reacts with the other. A general overview of the different cascades is shown in Figure 131.

- **Platelet aggregation** – This involves the activation of platelets and a blood protein which bind together via fibrin bridges. Drugs that act to block the activation of platelets are called anti-aggregation agents. Such drugs include aspirin and Sanofi-Aventis' Plavix.
- **Blood coagulation** – A series of reactions involving the activation of a number of inert proteins in plasma called blood factors (for example, Factor VIII and so on) culminate in the activation of fibrin, which creates a bridge between platelets. The heparins inhibit the activation of certain of these blood factors, so blocking the coagulation cascade. By acting on vitamin K, another molecule essential for coagulation, warfarin also inhibits blood factor activation.
- **Fibrinolysis** – Circulating blood contains factors that act to degrade the fibrin links between the platelets. In the clotting cascade, these are deactivated, enabling the clot to form. Drugs that act to enhance the degradation of fibrin include the tissue-type plasminogen activators or TPAs (e.g., Genentech's Activase).

Figure 131: Three pathways are involved in the creation of a thrombus



Source: Rang, Dale & Ritter

Figure 132: Summary of the main anti-thrombotic agents

Broad class	Heparins	Anti-aggregation agents	Fibrinolytics
Sales in 2004	$3.3bn	$6.7bn	$0.5bn
Pathway	Inhibit activation of blood factors	Inhibit activation of platelets	Encourage creation of plasmin
Key Products	Lovenox, Fragmin, Fraxiparine	Aspirin, Plavix, ReoPro	Activase, Retavase
Administration	Injection	Oral/injectable	Injection
Adverse effects	Haemorrhage, cytopaenia	Rash, diarrhoea, haemorrhage	Haemorrhage

Source: Deutsche Bank

Pharmacological treatment

Given the different pathways, several classes of drug have been developed in an effort to inhibit thrombosis:

Warfarin: The most commonly used anti-coagulation agent. Discovered in the 1920s, the product has been generic for many years (although BMS still realises $250m from its brand Coumadin). Warfarin acts by inhibiting the reduction of a key enzyme in the clotting process, vitamin K (K for *Koagulation* in German). In doing so, warfarin prevents the activation of

several clotting factors, namely II, VII, IX and X. However, the therapeutic use of warfarin requires a careful balance between giving too much (risk of bleeding) and too little (coagulation remains unchecked). Use is further complicated by the time taken for the drug to become active (two days) and because of numerous drug-drug interactions that alter its activity. The effect of warfarin is monitored by measuring the time taken to create Factor II (prothrombin) and is expressed as an International Normalised Ratio (INR). Dosage is usually adjusted to give an INR of 2-4 depending on the clinical situation.

Anti-aggregation agents: Anti-aggregation agents work at different stages of the pathway that leads to the combination of platelets with fibrin as illustrated in Figure 131. Several are taken orally and can be used as prophylactics (preventatives), reducing the risk of thrombosis and coronary events (aspirin is probably the best known example). A key area of recent interest has been the glycoprotein IIb/IIIa receptor on activated platelets, which binds fibrin.

Figure 133: Anti-aggregation agents

Brand name	Generic name	Producer	Sales 2004
Plavix	Clopidogrel	Sanofi-Aventis/BMS	$5.1bn
Reopro	Abciximab	Lilly	$0.4bn
Ticlid	ticlopidine	Sanofi-Aventis	<$0.1bn
Integrilin	eptifibatide	Schering-Plough/GSK	$0.3bn

Source: Company data

Heparins: One of the oldest classes of drug, heparins are long-chain sugar molecules (polysaccharides) that bind to the many different blood-clotting factors (e.g. Factor XII, Factor X). In doing so, they inhibit the clotting cascade. Today, heparin fragments, referred to as low molecular weight heparins (LMWH), are increasingly used. This is because they have a longer elimination period and, as such, their clotting effect is more predictable.

Figure 134: The heparins

Brand name	Generic name	Producer	Sales 2004
Lovenox	enoxaparin	Sanofi-Aventis	$2.4bn
Fraxiparine	nadroparin	GlaxoSmithKline	$0.4bn
Fragmin	dalteparin	Pfizer	$0.3bn
Arixtra	fondaparinux	GlaxoSmithKline	<$0.1bn

Source: Company data

Fibrinolytics: The smallest class of anti-thrombotic drugs, fibrinolytics, typically need to be injected quickly after the onset of symptoms (i.e. they are taken in response to trauma). However, by deactivating the clotting, their main drawback is that they can cause severe bleeding and gastric haemorrhage. The largest drugs in the class are Genentech's Activase and TNKase, with combined sales of just under $0.2bn.

Clinical end-points

The key endpoints used to assess the performance of anti-thrombotic agents are the reduction in the incidence of clotting or thrombo-embolic events compared to placebo. Additionally, bleeding as a side effect is also a very important consideration and anti-thrombotic agents should not significantly increase the risk of (potentially) uncontrollable bleeding.

Pipeline products

Given the importance of the anti-thrombotic market and its potential for growth, anti-clotting agents have been a keen area of interest for many pharmaceutical companies. The most recent pipeline hopeful to come before regulatory authorities was AstraZeneca's Exanta, an oral anti-coagulant intended to serve as a replacement for warfarin for the prevention of

stroke in patients with atrial fibrillation (irregular heart beat). However, the drug was deemed "not approvable" by the US FDA and delayed in Europe primarily due to concerns over potential liver toxicities. That said, physician support for the convenience of the drug was strong (it does not require the rigorous INR monitoring nor does it have the numerous drug-drug interactions or other side effects of warfarin), and AstraZeneca and other companies (e.g., GlaxoSmithKline, Boehringer Ihgelheim) are advancing additional oral molecules that target the same thrombin pathway inhibited by Exanta.

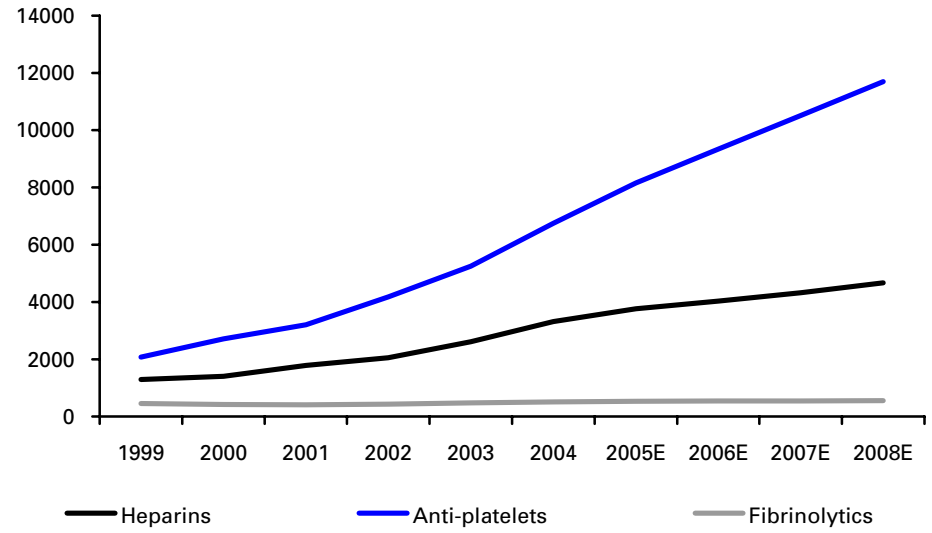
Also gaining increased attention are new oral compounds that inhibit Factor Xa, such as Bayer's BAY59-7939 and Bristol-Myers' razaxaban, both of which have shown a good safety profile and low bleeding risk in early clinical trials. In the anti-platelet field, Lilly and Sankyo are advancing a Plavix look-alike, prasugrel, which due to its higher affinity for the ADP receptor offers a more consistent anti-clotting benefit and works in a subset of patients where Plavix is ineffective.

Figure 135: Selected pipeline products for thrombosis

Name	Sponsor	Mechanism	Status	Est filing
Exanta	AstraZeneca	Direct thrombin inhibitor	"Not approvable"	Filed
prasugrel	Lilly/Sankyo	Platelet antagonist	Phase III	2006
idraparinux	Sanofi-Aventis	Factor Xa inhibitor	Phase III	2006
BAY59-7939	Bayer	Factor Xa inhibitor	Phase II	2007
razaxaban	Bristol-Myers Squibb	Factor Xa inhibitor	Phase II	2007
BIBR1048	Boehringer Ingelheim	Thrombin inhibitor	Phase IIb/III	2007
Odiparcil	GSK	Indirect thrombin inhibitor	Phase II	>2007
AZD6140	AstraZeneca	Platelet antagonist	Phase II	>2007
AZD0837	AstraZeneca	Direct thrombin inhibitor	Phase II	>2007
LY517717	Lilly/Amgen	Factor Xa inhibitor	Phase II	>2007

Source: Deutsche Bank

Figure 136: Sales growth of anti-thrombotic drugs ($ m)



Source: Wood Mackenzie

Figure 137: Sales growth of anti-thrombotic drugs ($ m)

	1999	2000	2001	2002	2003	2004	2005E	2006E	2007E	2008E
Heparins	1293	1405	1792	2056	2620	3319	3763	4039	4320	4665
Anti-platelets	2081	2710	3208	4174	5255	6750	8155	9346	10509	11694
Fibrinolytics	453	419	414	439	479	513	532	544	551	555

Source: Deutsche Bank

Erectile dysfunction

- 150 million men affected by ED worldwide, with prevalence expected to double by 2025
- Sales of PDE-V inhibitors including Viagra (Pfizer), Cialis (Lilly) and Levitra (Bayer) exceeded $2.2bn in 2004

An estimated 30 million men in the US and as many as 150 million men worldwide experience erectile dysfunction (ED), defined as the inability to achieve and maintain an erection adequate for satisfactory sexual intercourse. Causes of ED may be either physiological, psychological or (in the majority of cases) a combination of both. While an overwhelming 70% of cases are associated with vascular disease, ED may also be caused by drug-related, operative, neurological and other factors. In addition, ED often occurs as a consequence of normal aging, affecting as many as 50% of men between the ages of 40 and 70.

Physiology

In general terms, when a man is sexually aroused, the arteries in the penis muscles, the corpora cavernosa, relax and widen, allowing more blood to flow into the penis. At the same time, the veins in the muscles compress, restricting the blood outflow. With increased blood flow in and reduced blood flow out, the penis enlarges, resulting in an erection.

On a cellular level, this process is more complex. Upon stimulation, the corpora cavernosa muscles release the neurotransmitter nitric oxide (NO). NO in turn stimulates the enzyme guanylate cyclase, thereby facilitating the synthesis of cyclic guanine monophosphate (cGMP). Cyclic GMP triggers a cascade of reactions that eventually instruct the penile muscles to relax, allowing the blood accumulation required for erection.

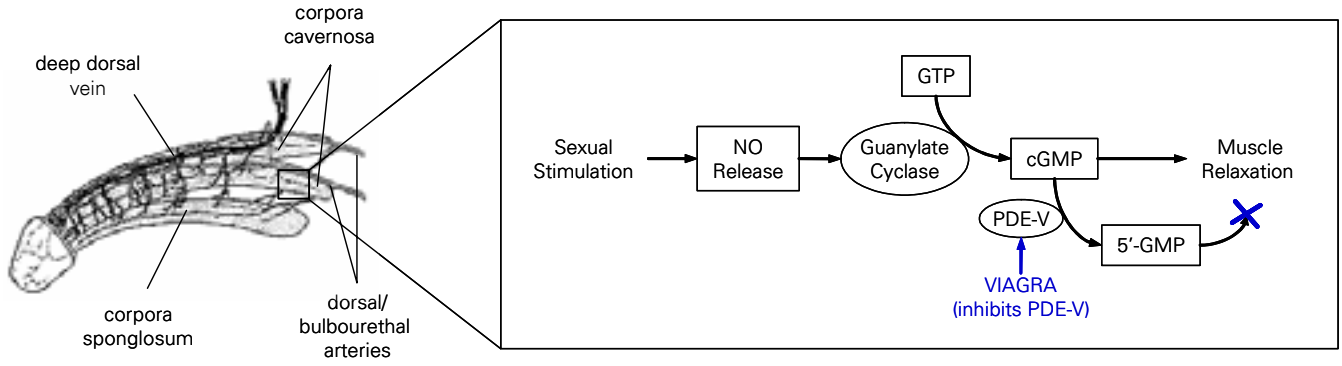
The natural regulator of this process is the enzyme phosphodiesterase type V (PDE-V). PDE-V inhibits erection by breaking down cGMP into a non-biologically active form, 5'-GMP. In the absence of cGMP, the body's signal to the corporate cavernosa is interrupted and the patient fails to achieve an erection.

Pharmacological treatment

Historically, ED was a relatively small market that lived under the domain of urological specialists. Drug therapies, using compounds such as phentolamine, papaverine and alprostadil, were either injected into the penis or delivered as urethral suppositories. Not until Viagra (sildenafil) was launched in 1998 did the therapeutic market for ED explode.

Viagra, together with newer entrants Cialis and Levitra, acts as a PDE-V inhibitor, blocking the enzyme's ability to inactivate cGMP. However, it has no effect on the initial release of NO. The implication of this is that Viagra can potentiate an erection once sexual stimulation has induced NO-release but the drug cannot produce an erection independently.

Figure 138: Mechanism of erection and action of PDE-V inhibitors



Source: National Institute of Diabetes & Digestive & Kidney Diseases

Viagra's adverse effects are in part associated with its interaction with other members of the phosphodiesterase family. There are 11 PDE isoforms in the body, each of which has an important role in other signalling pathways. Viagra appears to be many thousand-fold more selective for PDE-V than for most other PDE isoforms, including PDE-III, an isoform involved in the control of cardiac contractility. However, Viagra's selectivity for PDE-V versus PDE-VI (an isoform found in the retina) is only ten-fold greater, most likely forming the basis for colour vision disturbances seen in some patients. Both Levitra and Cialis avoid this side-effect due to their greater selectivity for the PDE-V isoform.

More importantly, the PDE-V inhibitors have been shown to enhance the hypotensive (blood-pressure lowering) effects of nitrate drugs often taken for heart conditions. Thus, they are contraindicated in this group of patients and are additionally discouraged in men with a recent history of coronary heart disease.

Figure 139: PDE-V inhibitors for erectile dysfunction

Name	Generic	Company	2004 Sales
Viagra	Sildenafil	Pfizer	$1.7bn
Cialis	Tadalafil	Lilly/ICOS	$0.6bn
Levitra	vardenafil	Bayer/Schering-Plough/GSK	$0.3bn

Source: Deutsche Bank

Clinical end-points

The severity of ED is typically evaluated using the Sexual Encounter Profile (SEP), a standardised questionnaire comprising a series of questions concerning sexual function. Two of the SEP questions usually serve as primary end-points, namely, those regarding: 1) the ability to achieve erections sufficient for sexual intercourse and 2) the maintenance of erections after penetration.

Figure 140: Efficacy and pharmacokinetic data for PDE-V inhibitors

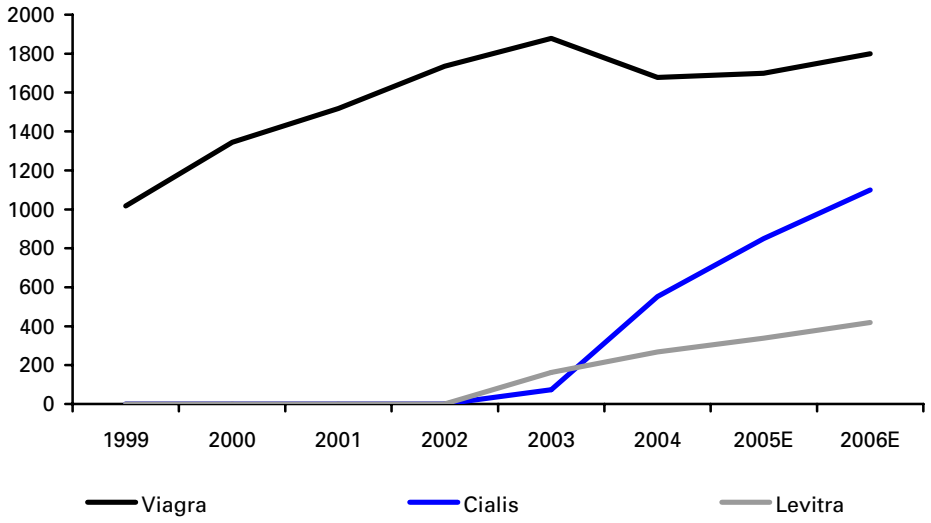
	Viagra (50 mg)	Cialis (20 mg)	Levitra (20 mg)
Producer	Pfizer	Lilly	Bayer/Schering-Plough/GSK
Generic	sildenafil	tadalafil	vardenafil
% erection sufficient for penetration (placebo)	74% (24%)	62% (39%)	80% (52%)
% maintenance of erection (placebo)	66% (20%)	50% (25%)	65% (32%)
Tmax (hours)	1.0	2.0	0.7
T½ (hours)	4.0	17.5	4-5
Selectivity for PDE-V vs. PDE-III	4,000x	44,000x	3,600x
Side effects	headache, flushing, dyspepsia, rhinitis, abnormal vision	dyspepsia, back pain, dizziness, myalgia	headache, flushing, rhinitis, dyspepsia

Note: All PDE-V inhibitors are contraindicated in patients with heart conditions who are taking or expect to take nitrates.
Source: Company data

Pipeline products

Given that Viagra, Cialis and Levitra already provide such an effective and convenient treatment of ED, there is little of consequence in the development pipeline. Tanabe and Vivus are developing TA-1790, a new PDE-V inhibitor that has been shown in animal models to cause a significantly smaller decrease in systemic blood pressure as compared to Viagra when co-administered with nitrates. While this could provide a safety advantage over the currently marketed PDE-Vs, we expect the class as a whole will continue to be contraindicated in patients with heart conditions.

Figure 141: Sales growth of key ED drugs ($ m)



Source: Company data, Deutsche Bank estimates

Figure 142: Sales growth of key ED drugs ($ m)

		1999	2000	2001	2002	2003	2004	2005E	2006E
Viagra	Pfizer	1017	1344	1518	1735	1879	1678	1700	1800
Cialis	Eli Lilly/ICOS	0	0	0	0	74	552	850	1100
Levitra	Bayer/GSK	0	0	0	0	163	268	339	418

Source: Deutsche Bank

NOTES

Gastrointestinal disorders

- World market in 2004 for ulcers and GERD worth $16bn
- Between 25-35% of US population affected by GERD
- Market dominated by proton pump inhibitors, including AstraZeneca's Nexium and Takeda/Abbott's Prevacid
- Underlying prescription growth (ex-omperazole) strong but value growth slowed by generic penetration

Both ulcers and gastro-oesophageal reflux disease (GERD) are disorders that arise as a consequence of stomach acid, causing tissue destruction or irritation. An ulcer is a focal area of the stomach or duodenum that has been destroyed by digestive juices and stomach acid, usually facilitated by the bacteria Helicobacter pylori (H.pylori) but often by the use of non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin, or from stress. Approximately 10% of Americans will develop a chronic peptic ulcer during their lifetime. GERD or heartburn refers to the backward flow of acid from the stomach up into the oesophagus, which, unlike the stomach, has no protective lining. Approximately 10% of Americans suffer from heartburn daily, with more than one-third of the population having intermittent symptoms.

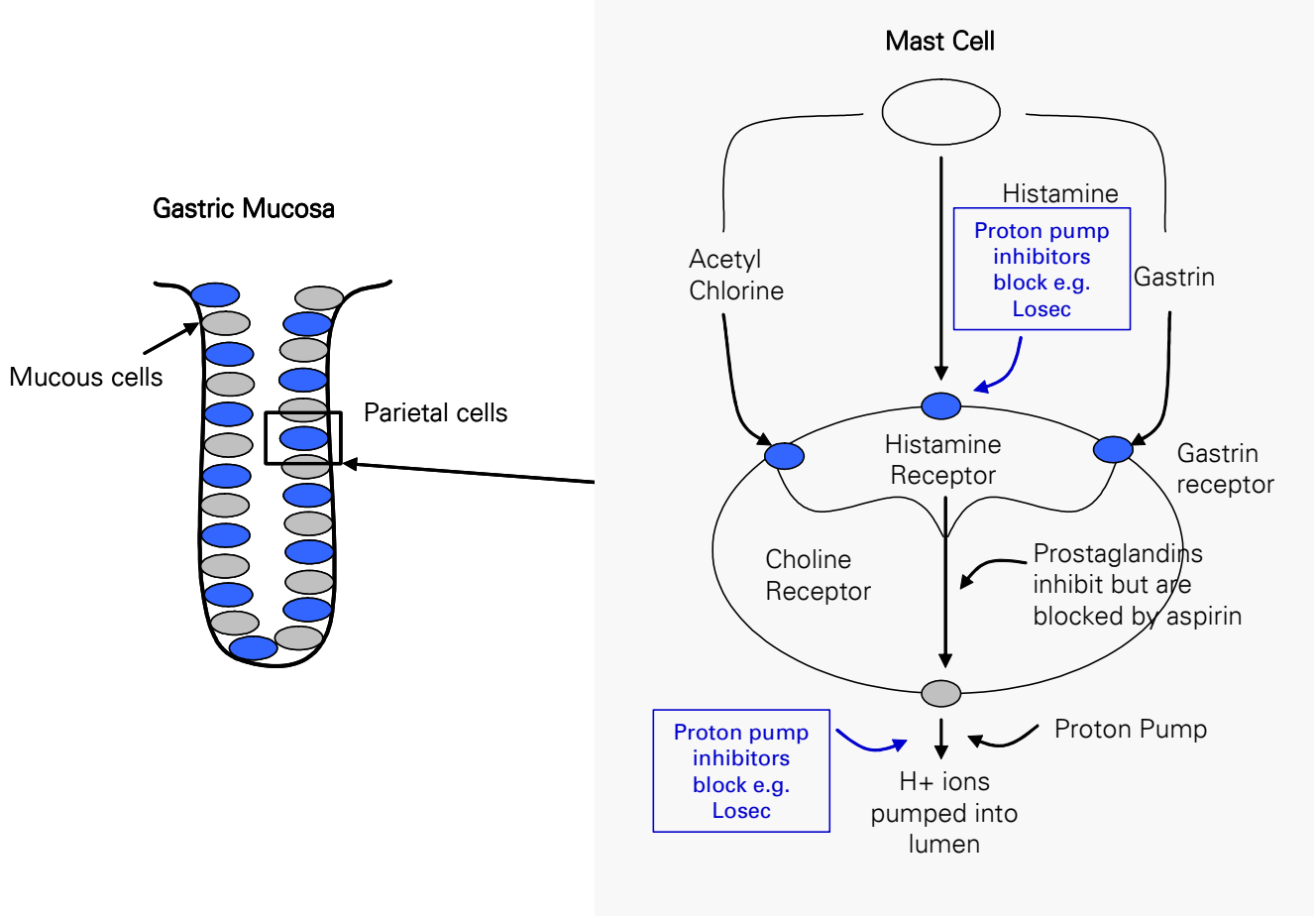
Physiology

The stomach secretes about 2.5 litres of gastric juice daily. The principal secretions are pepsinogens, used to break down proteins and hydrochloric acid, which serves to digest food and which is secreted by cells located in the stomach lining, called the parietal cells. In addition, mucus is secreted by mucosal cells and forms an important buffer protecting the gastric lining or mucosa from the acid attrition of the gastric juices. Locally produced prostaglandins stimulate the production of mucus (it is worth noting that by inhibiting one of the enzymes in prostaglandin production, namely cyclooxygenase 1, aspirin among other NSAIDs has a detrimental effect on the stomach).

In both ulcers and GERD, the regulation of acid secretion by the parietal cells is especially important and it is here that the main drugs act. Stimulation of the parietal cells by one of three main messengers encourages them to pass hydrogen ions via a 'proton pump' into the stomach. The three main biochemical messengers that promote the activity of the proton pump by acting on receptors located on its surface are illustrated in Figure 143. They include:

- Gastrin, a peptide hormone, which is synthesised in the mucosa and whose production is stimulated when food is digested in the stomach,
- Acetylcholine, which is released by nerve endings in the stomach upon the sight and smell of food, and
- Histamine. Both acetylcholine and gastrin act to cause histamine release from cells called mast cells, located close to the parietal cell. The histamine released then binds to histamine receptors (called H2 receptors) on the parietal cell and stimulates the proton pump to promote acid generation.

Figure 143: The parietal cell and action points for gastrointestinal action



Source: Rang, Dale & Ritter

Pharmacological treatment

In both GERD and peptic ulcers, one of the key aims of pharmaceutical therapy is to reduce or inhibit the production of acid, so preventing the stomach from digesting itself and allowing the damaged area of the mucosal wall to heal. The market is dominated by two main classes of drug, the H2 antagonists (for example, GSK's Zantac), which were first introduced in the 1970s, and the more recently introduced proton pump inhibitors or PPIs (for example, AstraZeneca's Losec). In the case of ulcers, an antibiotic may also be taken, typically in combination with a proton pump inhibitor, to eradicate the *Helicobacter pylori* bacterium. Because proton pump inhibitors directly inhibit acid production, they have proven significantly more efficacious in reducing acid levels, thereby increasing healing rates. Consequently, they account for a greater share of the market in volume terms. Patent expiry of the two leading H2 antagonists (GSK's Tagamet and Zantac) also means that by value, the PPIs dominate (albeit patent expiry of several products in this class has caused a sharp fall in its value share as well).

Figure 144: H2 antagonists and PPIs – some details

Class	H2 antagonists	PPIs
Estimated value in 2004	$1.8bn	$16.4bn
Leading products	Zantac	Nexium, Prevacid
Point of action	Histamine receptors	The proton pump
Healing rates 4 weeks	56% gastric ulcers healed	78% gastric ulcers healed
Healing rates 8 weeks	78% healing	91% healing

Source: Deutsche Bank estimates and company information

H2 antagonists: These completely inhibit histamine- and gastrin-related acid secretion but only partially decrease acetylcholine-related secretion (hence, they are less efficacious than PPIs). They are taken orally once or twice a day and are well tolerated. Side effects are limited, but include diarrhoea and dizziness. Most H2 antagonists are also available in over-the-counter formulations.

Figure 145: Leading H2 antagonists

Brand name	Generic name	Manufacturer	2004 sales
Zantac	ranitidine	GlaxoSmithKline	$0.5bn
Gaster	famotidine	Yamanouchi	$0.6bn
Pepcid	famotidine	Merck	<$0.1bn

Source: Company data

Proton pump inhibitors (PPIs): The PPIs irreversibly inhibit the proton pump in the parietal calls. First to market was Prlosec/Losec (omeprazole), which for several years was the world's best-selling drug but now faces generic competition. The product is taken orally but because it rapidly degrades in acid, it is administered with a special coating to ensure its absorption into the blood. Again, side-effects are rare but may include diarrhoea, headache and sometimes rash.

Following the arrival of generic omeprazole, value growth of the PPI class declined, whilst volume growth – including that of new entrants Protonix and Nexium – has remained strong. However, growth has again come under pressure following the launch of an OTC version of Prilosec (marketed by Procter & Gamble) in September 2003. Since that time, total PPI growth has been relatively flat but this mostly reflects declining prescriptions for omeprazole. In contrast, growth of the prescription PPIs ex-omeprazole has stabilised around 9-12%.

Figure 146: Leading PPIs

Brand name	Generic name	Manufacturer	2004 sales
Losec/Prilosec	omeprazole	AstraZeneca	$1.9bn
Prevacid	lansoprazole	Takeda/Abbott	$2.7bn
Nexium	esomeprazole	AstraZeneca	$3.9bn
Protonix/Pantozol	pantoprazole	Wyeth/Altana	$3.0bn
Aciphex/Pariet	rabeprazole	Johnson & Johnson/Eisai	$1.9bn
Takepron	lansoprazole	Takeda	$0.4bn
Zoton	lansoprazole	Wyeth	$0.4bn

Source: Company data

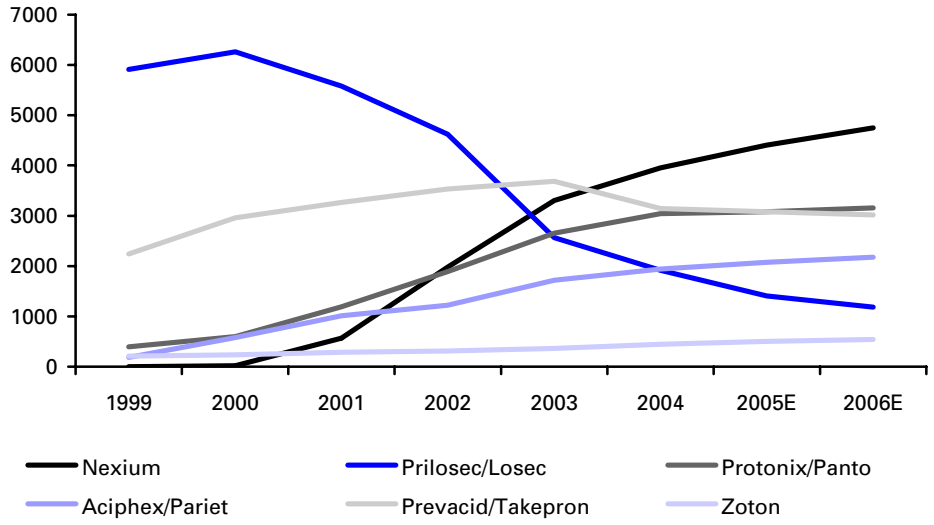
Clinical end-points

The key end-points used in clinical trials are typical rates of healing over different time periods compared to placebo. For gastric ulcers, the time periods used are typically four and eight weeks. For GERD and duodenal ulcers, healing over four to eight weeks is also measured. In addition, measures of stomach acidity over a set number of days may also be measured, although these are not indicative of healing rates.

Pipeline products

Given the $18bn in annual sales shared primarily by the PPIs and H2 antagonists, the GERD and ulcer market is obviously very attractive. However, the current PPIs are highly effective, leaving little room for significant improvement. Moreover, the market continues to be hugely competitive and with the availability of generic omeprazole contributing to increased price competition across the class. Thus, it is perhaps no surprise that the pipeline for gastrointestinal disorders is relatively thin and unexciting. Nonetheless, Altana is advancing soraprazan, which is an acid pump antagonist that reversibly inhibits both active and non-active pumps and does not require initial acid activation. However, AstraZeneca recently discontinued development of its reversible PPI, AZD0865, noting the limited incremental benfit that the novel mechanism appeared to offer relative to that seen with the traditional PPIs. Also of note, Novartis is currently conducting Phase III trials of its irritable bowel syndrome drug Zelnorm for the treatment of GERD.

Figure 147: PPI sales growth ($ m)



Source: Company data, Deutsche Bank estimates

Figure 148: PPI sales growth ($ m)

		1999	2000	2001	2002	2003	2004	2005E	2006E
Nexium	AstraZeneca	0	17	568	1978	3302	3949	4403	4748
Prilosec/Losec	AstraZeneca	5909	6260	5578	4623	2565	1918	1406	1184
Protonix/Panto	Altana/Wyeth	393	598	1187	1889	2657	3041	3080	3155
Aciphex/Pariet	Eisai/J&J	184	578	1011	1220	1721	1943	2076	2178
Prevacid/Takepron	Takeda/Abbott	2241	2960	3266	3533	3684	3145	3079	3018
Zoton	Wyeth	208	234	284	309	363	448	500	540

Source: Deutsche Bank

Asthma

- Worldwide market worth nearly $13bn in 2002
- Industry estimates that 5-7% of the population affected
- Market growing at over 11% per annum, aided by increasing diagnosis and more aggressive treatment
- Complicated delivery devices afford some revenue protection beyond drug patent expiry
- Leading companies include GlaxoSmithKline, Schering-Plough and AstraZeneca

Asthma is defined as a reversible obstruction of the airways, usually triggered in response to an allergic reaction. The asthmatic reacts to stimuli that are not of themselves noxious and suffers intermittent but recurrent attacks that consist of difficulty in breathing out due to severe constriction of the airways (bronchospasm). Patients frequently have a persistent cough and suffer mucus plugging of airways. Asthma is an increasingly common ailment, the incidence of which is believed to be growing, reflecting increased industrialisation, air pollution and urban living. It is a leading cause of hospitalisation and, perhaps surprisingly, it is estimated that as much as a third of the adolescent population suffering from asthma have not yet been diagnosed.

Physiology

The characteristic features of asthma are inflammatory changes in the respiratory airways that are associated with abnormal bronchial (lung) sensitivity to allergens that are normally non-noxious. For example, pollen, or particles of house-mite dust can provoke an asthma attack. Indeed, even the 'shock' of cold air can bring on an attack. Asthma's development probably involves both genetic and environmental factors.

Importantly, current theory suggests that there are two main phases to the attack:

- the initial response, which is the abrupt bronchospasm in response to the allergen; this involves the constriction of the smooth muscle in the bronchi
- the inflammation stage, which occurs after continued exposure to the allergen

The inflammation associated with asthma is different from bronchitis, in that it is associated with the presence of white blood cells (T cells), which release chemical messengers (cytokines), which in turn release products that cause damage to the airways.

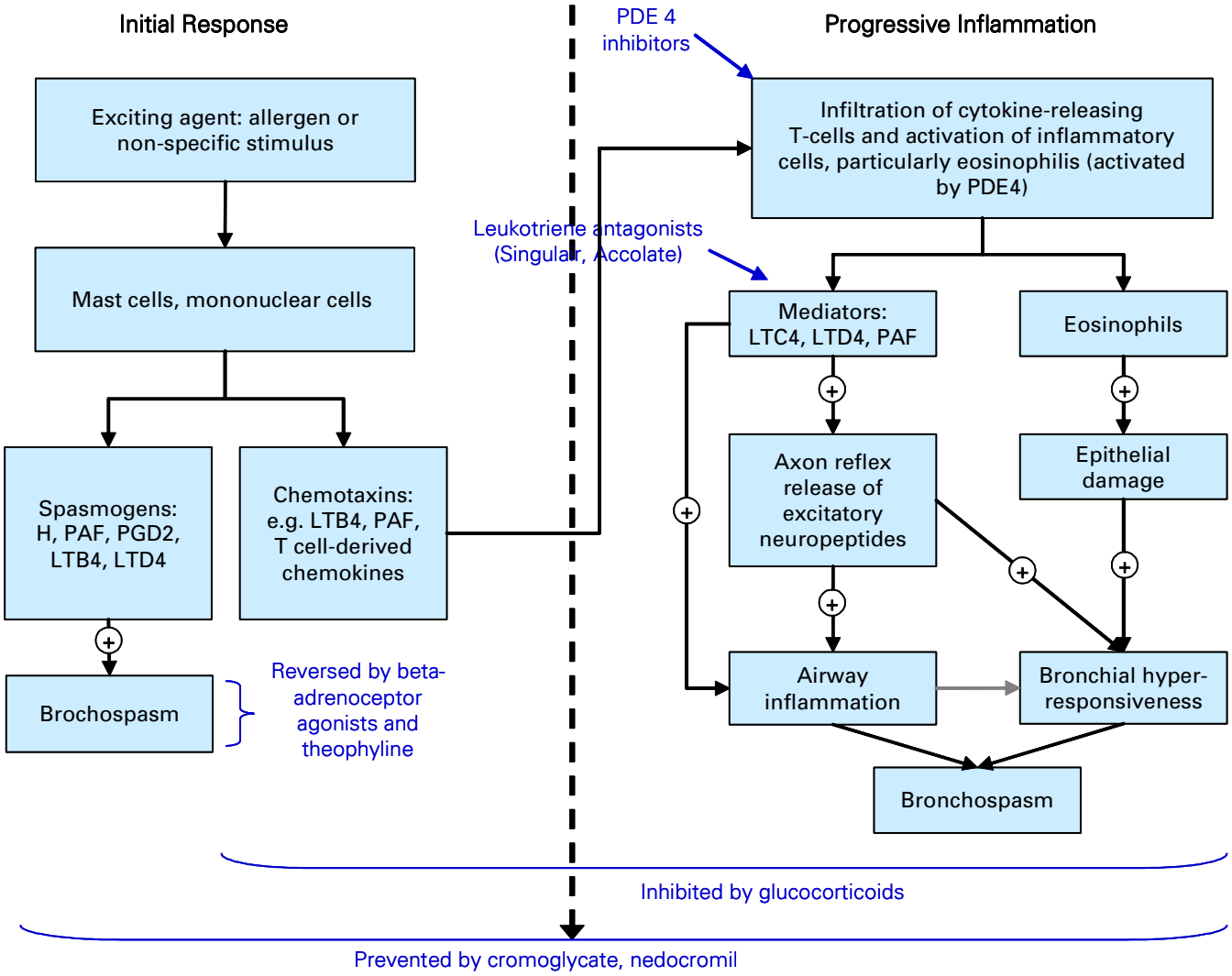
In the initial response, the bronchospasm arises as the allergen interacts with immune response cells called mast cells. These release histamines, which cause smooth muscle constriction. In addition and perhaps more significantly, potent bronchial-constrictors and inflammatory agents called leukotrienes are also released, attracting white blood cells to the area, so setting the scene for the delayed inflammation stage. Factors that activate platelets (PAF) and attract platelets to the area are also released from, among other things, the mast cells. Note that it is against this initial reaction that the beta agonists are used, acting on beta 2 receptors that are located in smooth muscle tissues in the lungs to cause vasodilation and so allow exhalation.

In the second or delayed phase, specific types of white blood cells, called T-helper lymphocytes (Th) and eosinophils (also a type of white blood cell), are released. Together with the leukotrienes, these cause inflammation. Specific molecules released by the eosinophils, which normally form part of the body's defences against bacteria, cause damage to the epithelial lining of the bronchi. This is believed to add to the sensitivity of the bronchi

by leaving the mast cells more exposed to allergens in the future. Because the synthesis of many of the inflammatory media, including PAF, the leukotrienes and prostaglandins, is initiated by precursors, whose synthesis is inhibited by steroids (the glucocorticoids), drugs based on glucocorticoids form the main pharmaceutical approach to both prevention and treatment of the inflammatory response.

A broad overview of the pathways and chemical mediators involved is shown in Figure 149.

Figure 149: The physiology of asthma


Initial Response
Progressive Inflammation
PDE 4 inhibitors
Exciting agent: allergen or non-specific stimulus
Infiltration of cytokine-releasing T-cells and activation of inflammatory cells, particularly eosinophilis (activated by PDE4)
Leukotriene antagonists (Singulair, Accolate)
Mast cells, mononuclear cells
Mediators: LTC4, LTD4, PAF
Eosinophils
Spasmogens: H, PAF, PGD2, LTB4, LTD4
Chemotaxins: e.g. LTB4, PAF, T cell-derived chemokines
Axon reflex release of excitatory neuropeptides
Epithelial damage
Brochospasm
Reversed by beta-adrenoceptor agonists and theophyline
Airway inflammation
Bronchial hyper-responsiveness
Bronchospasm
Inhibited by glucocorticoids
Prevented by cromoglycate, nedocromil

Source: Rang, Dale and Ritter

Pharmacological treatment

The treatment of asthma uses several different classes of drug, some of which are aimed at treating the initial bronchospasm, and others, the inflammatory response. A summary of the different classes and their areas of action are shown in Figure 150.

Figure 150: Leading asthma product classes

Class	Short-acting beta agonist	Long-acting beta agonist	Xanthines	Steroids (glucocorticoids)	Leukotriene antagonists
Acts on	Bronchospasm	Bronchospasm	Bronchospasm	Anti-inflammatory	Specific anti-inflammatory
Administration	Inhalation/oral/injected	Inhalation/oral	Oral/injected	Inhaled/oral	Oral
Use	Acute relief as required	In combination as prophylactic	Severe asthma	Prophylaxis	Relief and prophylaxis
Role	Initial therapy	Adjunct to steroids	Limited alternative	First line/add on	Alternative to steroids
Examples	Ventolin	Serevent, Oxis	Theo-Dur	Flovent/Flixotide	Singulair
Growth	Declining	Modest	Declining	Modest	Double digit
Novelty	Off-patent	Patented	Off-patent	Mixed	Novel

Source: Deutsche Bank

With a broad range of products available, treatment guidelines have been developed over the years. Updated in 1997, these give a useful indication of the approach to treatment of asthma. Important within the approach is the desire of physicians to direct treatment at the affected area, particularly given the use of steroids. As such, inhaled products that do not pass into the blood are often preferred to those taken orally. However, some element of any inhaled product will inevitably enter the blood system and, because steroids can reduce growth in children, US physicians have been reluctant to freely prescribe them for use in this patient group. However, superior performance has meant that these long-standing US concerns are gradually easing. This has further augmented the market share position of glucocorticoids, such as GlaxoSmithKline's Flovent.

Step 1: Inhaled short-acting beta agonist

Step 2: As in step 1, plus regular low-dose inhaled steroid or leukotriene antagonist (US only)

Step 3: As in step 1, plus regular high-dose inhaled steroid or regular standard dose inhaled steroid plus long-acting beta agonist.

Step 4: As in step 1, plus regular high-dose steroid, plus one or more of long-acting beta agonist, xanthine, sodium chromoglycate (for example, Intal), anti-muscarinic

Step 5 (severe): As in step 4, plus oral corticosteroid

Because treatment often involves the prescription of both an anti-inflammatory steroid and a bronchodilator, combination products are available. For example, GlaxoSmithKline's Advair/Seretide, which unites its long-acting beta agonist Serevent with its lead steroid, Flovent/Flixotide, has become a market leader with 2004 sales of over $4bn. With the exception of the xanthines and sodium cromoglycate, both of which are small and declining classes, the main drug classes are shown on the next page.

Product classes

- **Short- and long-acting beta agonists:** These work by stimulating the beta 2 receptors of the smooth muscle in the lungs. In doing so, they relieve the initial symptoms of asthma, that is, the inability to breathe. Taken by inhalation, they do little to treat the underlying inflammation. Their main side effect comes from their absorption into the blood and consequent action on beta 1 receptors outside the lungs, causing a tremor induced by vasoconstriction.

Figure 151: Leading short- and long-acting beta agonists

Brand name	Generic name	Producer	Sales 2004
Short Acting			
Ventolin	salbutamol	GlaxoSmithKline	$0.3bn
Bricanyl	terbutaline	AstraZeneca	$0.1bn
Proventil	albuterol	Schering-Plough	<$0.1bn
Long acting			
Serevent	salmeterol	GlaxoSmithKline	$0.6bn
Foradil	formoterol	Novartis/Schering-Plough	$0.3bn
Oxis	formoterol	AstraZeneca	$0.1bn

Source: Company data

- **Glucocorticoids (steroids):** These products act to inhibit the release of the factors that cause inflammation. Because they are not bronchodilators, they do not have any effect on smooth muscle. Their efficacy in management of chronic asthma is, however, unequivocal. They are given by inhalation through a metered dose inhaler. Because they are steroids, regular large doses can produce adrenal suppression, particularly in children, and it is this potential side effect that has historically restricted their popularity among US physicians. Indeed, it is the very low systemic absorption and complete first pass metabolism (breakdown by the liver) of Flixotide that have made it the inhaled steroid of choice.

Figure 152: Leading glucocorticoids (steroids)

Brand name	Generic name	Producer	Sales 2004
Flovent/Flixotide	fluticasone	GlaxoSmithKline	$1.1bn
Pulmicort	budesonide	AstraZeneca	$1.1bn
Becotide	beclomethasone	GlaxoSmithKline	<$0.1bn

Source: Company data

- **Leukotriene antagonists:** These products act on the inflammation cascade. Their appeal is that they act more specifically on the molecules that cause inflammation and, importantly, do not have the potentially worrying side-effects of steroids. However, their efficacy is modest. The leukotriene antagonists are taken orally and, because of their modest bronchodilator activity, are not used to treat bronchospasm.

Figure 153: Leading leukotriene antagonists

Brand Name	Generic name	Producer	Sales 2004
Singulair	montelukast	Merck	$2.6bn
Accolate	zafirlukast	AstraZeneca	$0.1bn

Source: Company data

- **Xanthines (theophyllines):** This class has long been used for bronchodilation. However, as newer products have been developed, the side effects associated with the xanthines have seen their use wane.
- **Combination products:** Given the popularity of prescribing both an anti-inflammatory steroid and a bronchodilator, several products combine these two compounds into a single drug.

Figure 154: Leading steroid/bronchodilator combination products

Brand name	Generic name	Producer	Sales 2004
Seretide/Advair	salmeterol/fluticasone	GlaxoSmithKline	$4.5bn
Symbicort	formoterol/budesonide	AstraZeneca	$0.8bn

Source: Company data

Clinical end-points

The two main clinical end-points used in asthma therapy are:

- FEV1 or the forced expiratory volume from the lungs emitted in one second. This measures the extent to which the bronchospasm has eased.
- PFER, or the peak expiratory flow rate, measures the maximal flow from the lungs in litres/minute after a full inhalation.

Pipeline products

Several new asthma drugs are in the pipeline. Many of these are based on inhibition of the inflammation cascade, looking to improve upon the benefit provided by currently available inhaled steroids. Amongst these are Schering-Plough's Asmanex and Altana/Sanofi-Aventis' Alvesco. Both are once-daily inhaled steroids but Alvesco's unique formulation gives it potentially the best safety profile in the class with minimal systemic side effects.

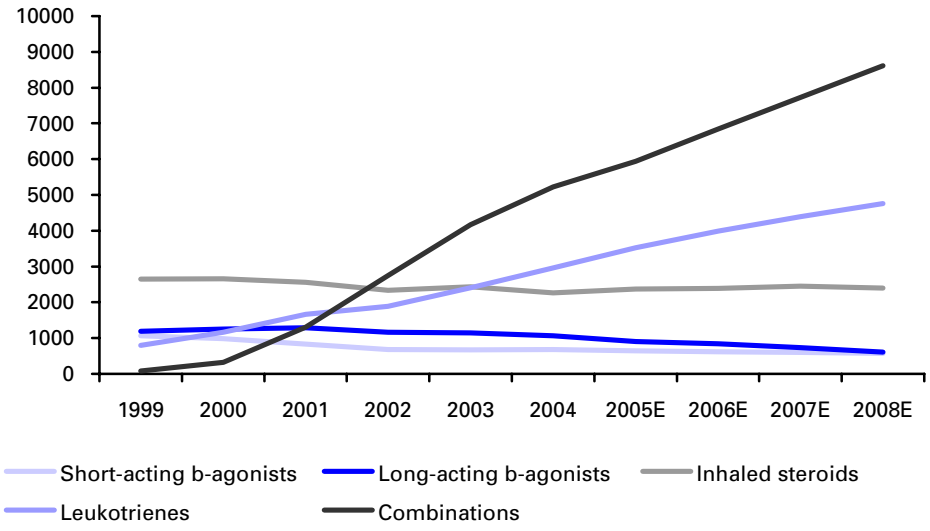
Amongst the other late-stage pipeline products, GlaxoSmithKline is developing a next-generation inhaled steroid and beta agonist, which it plans to formulate into a combination product to be positioned as a follow-on to Advair. Additionally, Altana is developing Daxas (roflumilast), a drug that could be first-to-market in a new class of respiratory drugs called PDE-IV inhibitors. In development for both asthma and COPD (see following section), Daxas has been filed in Europe and is expected to be filed in the US in 2006.

Figure 155: Selected pipeline products for asthma

Name	Sponsor	Class/Mechanism	Status	Est filing
Asmanex	Schering-Plough	Inhaled steroid	Launch 2005	Approved
Alvesco*	Altana/Sanofi-Aventis	Inhaled steroid	"Approvable"	Filed (US)
Daxas**	Altana	PDE IV inhibitor	Phase III (US)	2006 (US)
Symbicort*	AstraZeneca	Steroid + LABA	Phase III (US)	2006 (US)
arformoterol	Sepracor	Long acting beta agonist	Phase III	2005
QAB149	Novartis	Long acting beta agonist	Phase II	2007
R411	Roche	Dual integrin antagonist	Phase II	>2007
685698	GlaxoSmithKline	Inhaled steroid	Phase II	>2007
842470	GlaxoSmithKline	PDE IV inhibitor	Phase II	>2007
766994	GlaxoSmithKline	CCR3 antagonist	Phase II	>2007

*Source: Deutsche Bank *Approved and marketed in EU. **Filed in EU in February 2004.*

Figure 156: Sales growth for different classes of asthma drug ($ m)



Source: Wood Mackenzie

Figure 157: Sales growth for different classes of asthma drug ($ m)

	1999	2000	2001	2002	2003	2004	2005E	2006E	2007E	2008E
Short-acting b-agonists	1065	981	836	680	667	681	644	620	595	571
Long-acting b-agonists	1187	1253	1287	1165	1146	1069	901	838	730	604
Inhaled steroids	2648	2657	2558	2338	2434	2266	2369	2391	2449	2395
Leukotrienes	796	1167	1666	1890	2407	2965	3521	3987	4389	4761
Combinations	78	320	1307	2745	4165	5220	5935	6846	7727	8613

Source: Wood Mackenzie

Chronic obstructive pulmonary disorder

- Worldwide market for COPD estimated at $2.9bn
- Incidence growing at 12% per annum
- 24 million US adults affected by COPD but only 10m are diagnosed

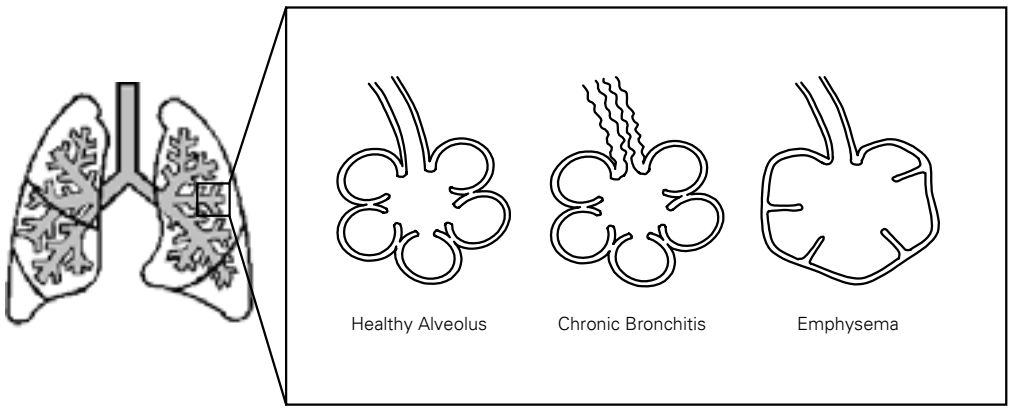
Chronic Obstructive Pulmonary Disorder (COPD) is a broad term covering several closely related respiratory diseases, including chronic bronchitis and emphysema. It is estimated to affect 5% of the population and is the fourth-leading cause of death globally. Cigarette smoking is the primary cause of COPD, responsible for 80-90% of all cases. While the prevalence of smoking has decreased in recent years, COPD is on the rise. This is explained by the fact that COPD develops only after many years of smoking, so we are just now seeing the effects of changes in smoking demographics from decades ago.

Physiology

Although both classified under COPD, chronic bronchitis and emphysema are distinct conditions with different symptoms and causes. Chronic bronchitis is associated with chronic coughing that produces excess mucus secretion into the bronchial tree. ("Chronic" is defined as occurring on most days for at least three months of the year and recurring over the course of at least two consecutive years). Caused by prolonged exposure to bronchial irritants, chronic bronchitis results in inflammation and narrowing of the airways.

Emphysema, on the other hand, is characterised by enlargement of the air sacs that lie at the ends of the bronchial branches in the lungs. Also caused by repetitive irritation, the normally elastic air sacs, called alveoli, become more rigid and the walls of the airways are destroyed. This tissue damage reduces the surface area in the sacs available for gas exchange, resulting in diminished breathing capacity.

Figure 158: Lung damage in COPD



Source: Deutsche Bank

Damage to the alveoli occurs due to destruction of elastin, a protein responsible for maintaining the strength of the alveolar walls. Smoking facilitates this process by stimulating production of elastase, a protein that degrades elastin. There is also a rare hereditary condition, known as "familial emphysema," that is characterised by genetic deficiency of α_1-antitrypsin (AAT). Because AAT normally inhibits the destructive effects of elastase, deficiency of this protein can lead to emphysema in otherwise low-risk non-smokers.

Pharmacological treatment

Despite the physiological differences between COPD and asthma, drug therapies for COPD have similar aims – to relax and open narrowed airways, to reduce inflammation and to loosen built-up mucus. The three primary groups of drugs are described below. (Also see previous section on asthma.)

- **Anticholinergics.** Anticholinergic drugs are generally used as a first-line therapy for COPD. They help facilitate bronchodilation by blocking the action of the neurotransmitter acetylcholine in the smooth muscle of the bronchial tree. Although fairly potent, anticholinergics are short acting and thus must be administered up to four times per day.

Figure 159: Leading anti-cholinergics

Brand name	Generic name	Producer	Sales 2004
Atrovent	Ipratropium	Boehringer Ingelheim	$0.5bn
Combivent	ipratropium/albuterol	Boehringer Ingelheim	$0.8bn
Spiriva	Tiotropium	Boehringer Ingelheim/Pfizer	$0.6bn

Source: Deutsche Bank

- **Long-acting beta agonists.** These drugs, developed primarily for asthma, facilitate bronchodilation by stimulating the beta 2 receptors found in the smooth muscle of the lungs.
- **Steroids.** Unlike the anticholinergics and beta agonists, these drugs target the inflammatory response by inhibiting the release of factors that cause inflammation.

Clinical end-points

Among the tools used to measure the severity of COPD is a factor called forced expiratory volume (FEV1). FEV1 measures lung function by calculating how much air a patient can exhale in one second. Although FEV1 decreases with age in healthy adults, this decline is two-to-three times more pronounced in patients with COPD. Consequently, an improvement in FEV1 versus placebo generally serves as a key endpoint in clinical studies.

Pipeline products

The size and growth potential of the COPD market, together with the fact that it is as yet poorly served, have encouraged companies to develop new treatments. In November 2003, GSK won FDA approval for use of its combination steroid/beta agonist asthma drug, Advair, in COPD. However, the formal approval provided only a modest boost to sales as an estimated 16-20% of prescriptions were already being used off-label.

More interesting is a novel class of drug that aims to relax airway muscles by inhibiting an enzyme known as phosphodiesterase IV (PDE-IV). PDE-IV normally breaks down cyclic adenosine monophosphate (cAMP), a molecule responsible for activating protein kinase, which in turn relaxes bronchial muscle. By inhibiting this process, PDE-IV inhibitors enable the production of more protein kinase, thereby enhancing bronchodilation.

Despite several development failures – namely at Bayer, Lilly and GlaxoSmithKline – companies have persisted with this class of molecules. One of the key challenges with the

PDE-IV inhibitors has been finding an optimal balance between efficacy and side effects. Whereas many of the failed candidates were able to show good efficacy, the dose level required was invariably associated with significant side effects (principally nausea and vomiting) that have prevented commercialisation.

Altana's Daxas (roflumilast) has managed to avoid this pitfall with 6% and 3% of patients reporting diarrhoea and nausea, respectively in the 24-week RECORD study. However, efficacy of the drug has been modest, with Daxas failing to match (let alone exceed) the FEV1 improvements seen with either Pfizer/Boehringer Ingelheim's Spiriva or GSK's Advair. Similarly, in the one-year RATIO study, Daxas demonstrated only a modest benefit on FEV1 but, importantly, failed to show a significant reduction in the rate of exacerbations.

Figure 160: Selected pipeline drugs for COPD

Name	Sponsor	Mechanism	Status	Est filing
Daxas*	Altana	PDE IV inhibitor	Phase III (US)	2006 (US)
842470	GlaxoSmithKline	PDE IV inhibitor	Phase II	>2007
ONO-6126	Ono Pharmaceutical	PDE IV inhibitor	Phase II	>2007
681323	GlaxoSmithKline	p38 MAP kinase inhibitor	Phase I	>2007

*Source: Deutsche Bank *Filed in EU February 2004.*

NOTES

Allergic rhinitis

- Prescription antihistamine market is worth nearly $5bn in 2004
- 40 million Americans are affected by allergic rhinitis
- Leading products include Clarinex (Schering-Plough), Allegra (Sanofi-Aventis) and Zyrtec (UCB/Pfizer)

Allergic rhinitis results from the body's hypersensitivity to normally innocuous particles which, when inhaled through the nose, elicit an adverse reaction. Allergic rhinitis may either be seasonal or perennial. Seasonal allergies, known as hay fever, arise following exposure to seasonal allergens (primarily pollens) that are present in the spring and/or autumn. Perennial allergic rhinitis is present year-round and is caused by non-seasonal allergens such as dust mites, animal hair or skin particles and moulds. Allergic rhinitis is estimated to affect more than 40 million Americans and ranks as the sixth most common chronic illness in the US.

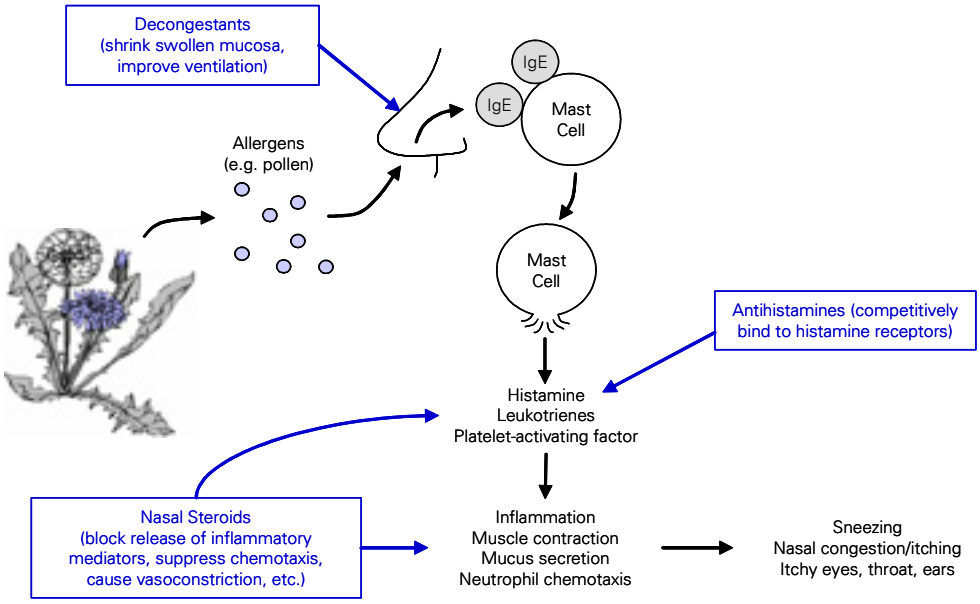
The allergy market has grown enormously in recent years, with the antihistamines alone leaping from $2bn in sales in 1997 to over $6bn in 2002. One of the key drivers of this growth has been the liberalisation of direct-to-consumer advertising in the US in 1997. Antihistamines have been one of the most heavily promoted drug categories with an approximate spend of $350m in 2003. However, the over-the-counter switch for class leader Claritin in late 2002 has seen this growth moderate, with further slowdown anticipated following the likely arrival of Allegra generics in 2006.

Physiology

Allergic rhinitis is triggered by exposure to normally innocuous substances that elicit an adverse immune reaction. There is strong evidence of a genetic component to the disease, with children of one allergic parent having a 30% risk of developing allergic rhinitis and children of two allergic parents having almost a 50% risk of becoming allergic. Allergen exposure is an additional predisposing factor. That is, in order to develop allergies, one must have an initial exposure to the appropriate allergen. Thus, many potential allergy sufferers may never develop symptoms because they never come into contact with the offending allergen.

Allergies are caused by an antibody-mediated immune reaction to specific allergens. Following initial exposure, allergen-specific IgE antibodies are produced that bind to certain immune cells, called mast cells, located in the nasal passage. Upon re-exposure, the mast cell-bound IgE molecules interact with the airborne antigen, triggering the release of inflammatory mediators such as histamine, leukotrienes, and platelet-activating factor (PAF) as shown in Figure 161. It is these agents that are responsible for the acute inflammatory response, along with increased mucus secretion, muscle contraction and other allergic symptoms. A further late-stage reaction may also occur in some patients following an influx of inflammatory cells such as eosinophils, monocytes and macrophages, which occurs hours after the initial exposure. These cells trigger similar allergic symptoms despite the absence of the original allergen.

Figure 161: Early-phase allergic reaction



Source: Dipiro, Talbert, Yee, Matzke, Wells and Posey

Pharmacological treatment

Although avoidance of the relevant allergens is the most direct method to prevent allergic rhinitis, not surprisingly, it is usually the most difficult given the widespread prevalence of many seasonal and perennial antigens. Immunotherapy, in which a patient undergoes repeated exposure to the allergen in an attempt to sensitise his or her immune system, may offer long-term benefit but its use is also limited given the significant expense, time commitment and potential risks involved.

Thus, treatment of allergic rhinitis primarily relies on pharmacological therapies, namely antihistamines, decongestants and steroids. Antihistamines are histamine receptor antagonists that competitively bind to H_1 histamine receptors, thereby inhibiting histamine-induced inflammation. Because antihistamines are better at preventing the actions of histamine rather than reversing the effects once they have taken place, they are best given prior to anticipated allergen exposure. Many of the first-generation drugs such as diphenhydramine HCl (Tavist) and clemastine fumerate (Benadryl) are available over the counter (OTC). While offering therapeutic benefit, drowsiness is often a chief complaint of patients taking these drugs. In addition, several first-generation drugs are associated with drug-drug interactions, a key factor that led to the withdrawal of Hoechst Marion Roussel's Seldane and J&J's Hismanal.

Given these problems with the first-generation antihistamines, the second-generation drugs have largely taken over the prescription market. Prior to 2002, the market leader was Schering-Plough's Claritin, with Sanofi-Aventis' Allegra and Pfizer/UCB's Zyrtec competing for second place and Schering-Plough's Clarinex a somewhat distant third. Although all drugs in the class are marketed as non-sedating, Zyrtec exhibits a higher sedation rate than the other two compounds.

In December 2002, however, Schering-Plough gained FDA approval to switch Claritin to OTC status shortly before generics were set to become available. While consumer efforts to force an OTC switch for the other prescription-only drugs have failed, the prescription market has come under pressure as many managed care organisations have shifted Allegra, Zyrtec and

Clarinex to the least-preferred formulary position (thereby increasing patient out-of-pocket co-pays) and certain seasonal users have switched to the OTC product.

Figure 162: Leading prescription antihistamines for allergic rhinitis

Name	Generic	Producer	2004 Sales
Claritin*	loratadine	Schering-Plough	$0.3bn
Allegra	fexofenadine	Sanofi-Aventis	$1.9bn
Zyrtec	cetirizine	UCB/Pfizer	$1.9bn
Clarinex	desloratadine	Schering-Plough	$0.7bn

*Source: Company data *Excludes US OTC sales .*

Given the nasal congestion often associated with allergic rhinitis, many patients also take a topical or systemic decongestant. Topical decongestants, available as drips or sprays, are highly effective and available OTC, contributing to their widespread use. While not as effective in terms of immediate onset of action, oral decongestants may last longer and cause less local irritation. In addition, Schering-Plough, Sanofi-Aventis and UCB (the makers of Claritin, Allegra, and Zyrtec, respectively) have all developed combined antihistamine/decongestant products, designated with a "D" (e.g., Claritin D), in an effort to provide added convenience to consumers.

Particularly for patients who suffer from perennial rhinitis, nasal steroids offer a third mode of treatment. These drugs, given as an intranasal spray, are most effective when administered ahead of exposure to allergens. However, therapeutic benefits may not be evident for several days, with peak responses usually appearing after two-to-three weeks.

Figure 163: Leading nasal steroids for allergic rhinitis

Name	Generic	Producer	2004 Sales
Flonase	fluticasone propionate	GlaxoSmithKline	$1.1bn
Nasacort	triamcinolone acetonide	Sanofi-Aventis	$0.3bn
Nasonex	mometasone furoate	Schering-Plough	$0.6bn
Rhinocort	budesonide	AstraZeneca	$0.4bn

Source: Company data

It is also important to note that Merck's Singulair (montelukast), a drug originally developed for asthma, has also been approved for seasonal allergic rhinitis. Singulair acts as a leukotriene antagonist, thereby inhibiting allergy symptoms via a different mechanism from the traditional antihistamines.

Pipeline products

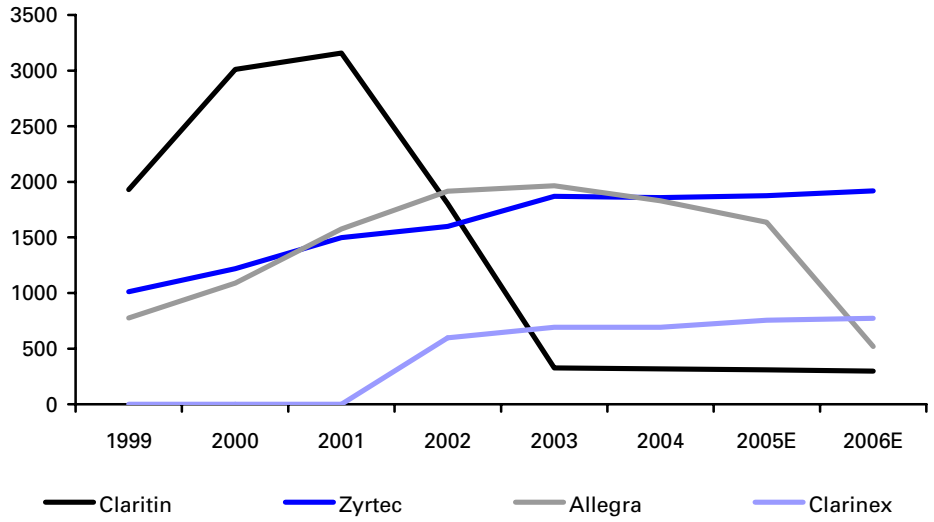
With the currently marketed antihistamines and inhaled steroids providing satisfactory relief for the majority of those suffering from allergic rhinitis, there is little demand for new drugs in this area. Nonetheless, several companies, including UCB and GSK, are developing improved antihistamines and steroids. Amongst these are UCB's Xysal, the single isomer of Zyrtec which is currently marketed in Europe and is expected to be filed in the US in 2006, and GSK's 685598, an intranasal steroid (also in development for asthma) that will serve as a follow-on to its $1bn drug Flonase, which is expected to face generics in the near future.

Figure 164: Key pipeline products for allergic rhinitis

Name	Sponsor	Class/Mechanism	Status	Est filing
Avamys/Allermist ('698)	GlaxoSmithKline	Intranasal steroid	Phase III	2006
Xysal	UCB	Antihistamine	Phase III	2006
Alvesco	Altana/Sanofi-Aventis	Intranasal steroid	Phase II/III	2006
766994	GlaxoSmithKline	CCR3 antagonist	Phase II	>2007
efletirizine	UCB	Antihistamine	Phase II/III	>2007

Source: Deutsche Bank

Figure 165: Sales forecast for leading antihistamines ($ m)



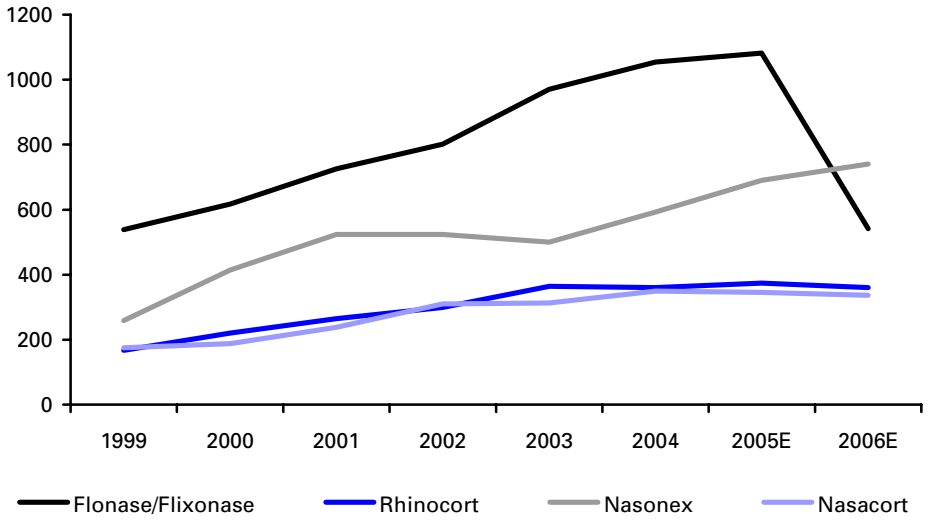
Source: Deutsche Bank estimates

Figure 166: Sales forecast for leading antihistamines ($ m)

		1999	2000	2001	2002	2003	2004	2005E	2006E
Claritin	Schering-Plough	1929	3011	3158	1802	328	320	310	300
Zyrtec	Pfizer/UCB	1014	1219	1498	1599	1868	1858	1874	1919
Allegra	Aventis	776	1089	1577	1914	1963	1830	1637	520
Clarinex	Schering-Plough	0	0	0	598	694	693	755	775

Source: Deutsche Bank

Figure 167: Sales forecast for leading nasal steroids ($m)



Source: Deutsche Bank estimates

Figure 168: Sales forecast for leading nasal steroids ($ m)

		1999	2000	2001	2002	2003	2004	2005E	2006E
Flonase/Flixonase	GlaxoSmithKline	539	617	726	802	970	1054	1082	541
Rhinocort	AstraZeneca	167	221	265	299	364	361	374	360
Nasonex	Schering-Plough	259	415	524	524	500	593	690	740
Nasacort	Aventis	176	188	238	310	313	349	345	337

Source: Deutsche Bank

NOTES

Osteoporosis

- World market in 2004 worth approximately $6.6bn
- Growth estimated at over 15%, driven by new drugs and demographics
- 80% of sufferers are women
- Key products include Merck's *Fosamax*, P&G/Sanofi-Aventis' *Actonel* and Lilly's *Evista*

Osteoporosis (literally porous bone) is a disease in which bones gradually become more porous and consequently weaker and more brittle. It is defined as a bone mineral density (BMD) that is at most only 40% that of a 'young normal adult' and generally progresses with age. Often accompanied by the distortion of bone structure, it is estimated that 10 million Americans suffer from the disease, while a further 18 million suffer from a milder reduction in bone density, termed osteopenia. Less than half of sufferers are currently receiving treatment.

Osteoporosis is associated with a high risk of bone fractures, bone pains and bone cancers if left untreated. With lifespans increasing and the elderly representing a greater proportion of the population, the financial burden of treating the disease is increasing quickly. Consequently, the demand for better medication to prevent or reduce the risk of osteoporosis-derived complications is high.

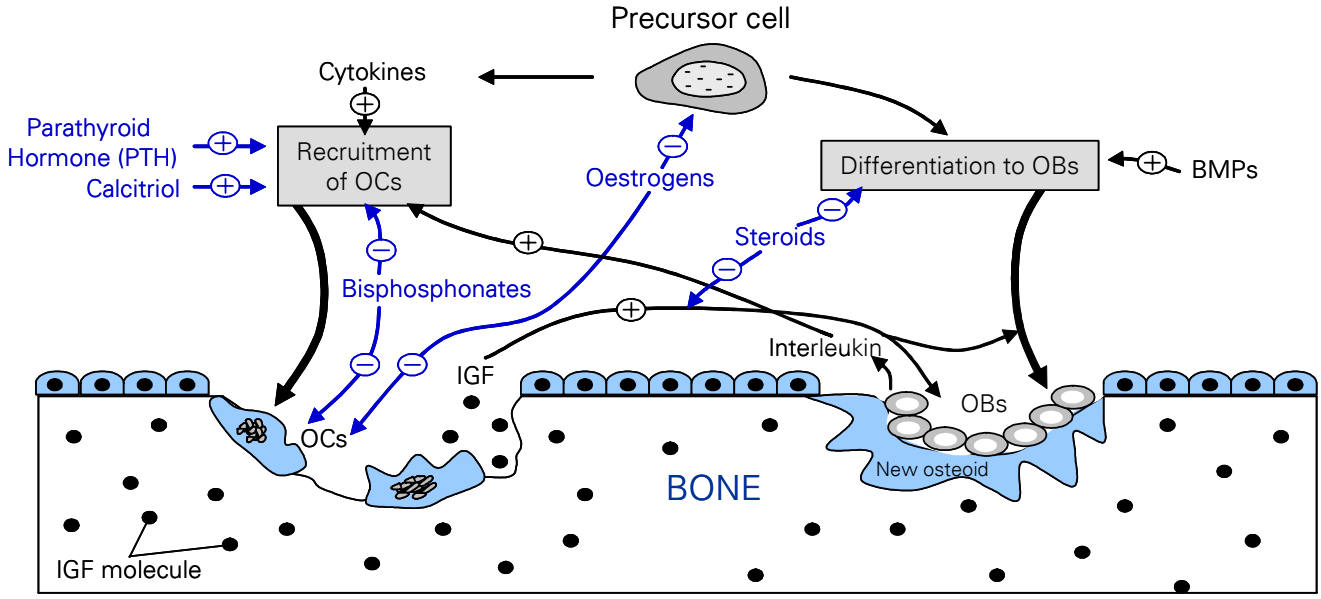
Physiology

Bone is predominantly comprised of collagen, calcium and phosphate ions, bound together by phosphoproteins. Simplistically, bone is created by the establishment of an organic collagen-based network or osteoid, onto which calcium phosphate crystals are deposited, so establishing a hard bone matrix. In healthy adults, the bone mass is continuously being remodelled, with some bone being resorbed and some new bone laid down. This process of remodelling is undertaken by two types of cells – osteoblasts, which secrete new bone matrix, and osteoclasts, which break it down – and is closely regulated by the action of hormones (including oestrogen, which dampens the activity of the osteoclasts) and other chemicals.

The process of bone remodelling is dynamic, although bone breakdown can be also initiated when bone is damaged or when plasma calcium falls below a particular level. Key to the process is the role of the parathyroid gland in maintaining plasma calcium concentrations. Receptors on the parathyroid cells react to a decline in the calcium concentration, triggering the secretion of parathyroid hormone (PTH), which then acts on a number of pathways. One of these pathways involves the breakdown of older bone, where PTH:

- Promotes the formation of the hormone calcitriol from vitamin D, which facilitates the formation of osteoclasts from precursor cells;
- Encourages the action of chemical messengers or cytokines, such as the interleukins on the osteoclasts, so stimulating their activity. The osteoclasts then adhere to the bone, move along it and secrete hydrogen ions and proteolytic (protein-cleaving) enzymes that break down bone and release its components, such as calcium and insulin-like growth factor (IGF1) from the site of their action.

Figure 169: Bone remodelling is dynamic



Source: Rang, Dale & Ritter Note: OCs are osteoclasts and OBs osteoblasts

It is the release of insulin-like growth factor that initiates the process of bone replacement and the second phase of the cycle. IGF1 stimulates the activation and formation of osteoblasts. Once activated, the osteoblasts migrate to the site of bone breakdown and, together with collagen-producing cells (called chondrocytes), produce the osteoid matrix in which the crystals of calcium phosphate are deposited to create new bone. In addition, the osteoblasts release interleukins that activate the osteoclast cells, so reinitiating the remodelling cycle.

Although the cycle is dynamic, there are several important regulatory mechanisms. These tend to regulate osteoclast activity.

- Increased plasma calcium concentration acts on receptors on the surface of the parathyroid cells and inhibits PTH secretion, thereby preventing further formation of osteoclasts.
- Oestrogen acts to inhibit the action of the interleukins that stimulate osteoclast activity, inhibits the development of osteoclast precursor cells and encourages the osteoclasts to undergo programmed cell death (apoptosis). Thus, the absence of oestrogen in post-menopausal women leads to an increased incidence of osteoporosis.
- Calcium levels also impact the activity of the hormone, calcitonin, with a rise in calcium concentration leading to an increase in calcitonin release. Calcitonin is secreted by the special "C" cells in the thyroid, which bind to a specific receptor on osteoclasts and stop further bone breakdown.

Osteoporosis is commonly found in:

- Post-menopausal women, whose oestrogen levels have fallen to the extent that control of the inhibition of osteoclast activation is reduced, and
- the elderly, whose bodies fail to rebuild bone that has been broken down as a result of factors such as a reduction in osteoblast activity, calcium uptake and so on.

Importantly, because excessive levels of steroids tend to inhibit the formation of osteoblasts and their activation, osteoporosis can also arise as a side effect of excessive use of steroids (glucocorticoids).

Pharmacological treatment

There are currently two major classes of compounds on the market for treating and preventing osteoporosis: the bisphosphonates and the selective oestrogen receptor modulators (SERMs). Other alternatives include oestrogen or hormone replacement therapies, which are largely used for prevention, and the calcitonins.

Figure 170: Osteoporosis treatment—SERMS and bisphosphonates compared

	Bisphosphonates	SERMs
Sales 2004	$4.5 bn	$1.4 bn
Leading product	Fosamax (Merck)	Evista (Eli Lilly)
Point of action	Inhibits osteoclast activation & promotes osteoclast apoptosis (death)	Inhibits osteoclast activation
Healing rates	Reduces the risk of one or more spine fractures by 47% and the risk of two or more spine fractures by 90%	Reduces the risk of first spine fracture by 55% and the risk of subsequent spine fractures by 30%
Side Effects	Musculoskeletal or abdominal pain, nausea, heartburn	Hot flushes, deep vein thrombosis

Source: Deutsche Bank, Company data

Bisphosphonates

With several products available, the bisphosphonates currently dominate the market for the treatment of osteoporosis. They work by inhibiting the activation of osteoclasts and promoting their programmed death (apoptosis), thereby reducing bone breakdown and reducing the risk of fractures. They are resistant to enzyme breakdown and are effective in reducing the level of bone loss in the elderly. The two leading products indicated for osteoporosis, Fosamax and Actonel, do, however, suffer from the major disadvantage of having to be taken 30 minutes before a meal with a full glass of water, after which time the patient must remain in an upright position. Gastrointestinal complaints such as ulcers are the main side effect. In an effort to minimise this inconvenience, the market for bisphosphonates has moved from once-daily to once-weekly dosing. The newest entrant, Roche/GSK's Boniva, just launched in April 2005, aims to reduce this schedule further by offering a once-monthly pill.

Note that Novartis' Aclasta (like its predecessor Aredia) is also a bisphosphonate but is currently not indicated for osteoporosis. Rather, it is approved (under the tradename Zometa) to treat the breakdown of bone due to metastatic cancer. However, Novartis is currently conducting Phase III studies for Aclasta in osteoporosis in an effort to gain official approval for this indication.

Figure 171: Leading bisphosphonates

Name	Generic name	Producer	2004 sales
Fosamax	alendronate	Merck	$3.2bn
Actonel	risedronate	Sanofi-Aventis	$1.3bn
Boniva	ibandronate	Roche/GSK	launch

Source: Company data

Selective oestrogen receptor modulators (SERMs)

There is only one SERM currently on the market – Lilly's Evista. This product mimics the action of oestrogen by binding to specific oestrogen receptors on osteoclasts, slowing the rate of bone loss. In addition, Evista is currently in Phase III clinical trials for prevention of breast cancer. We believe that, if successful, Evista could increasingly take market share from the bisphosphonates on account of this broader indication.

Figure 172: SERMs on the market

Name	Generic name	Producer	2004 sales
Evista	raloxifene	Eli Lilly	$1.0bn

Source: Company data

Clinical end-points

The objective of all therapies for osteoporosis is to increase bone density, decrease or stop bone loss and reduce the risk of bone fractures. Phase III clinical trials are usually run for three years. Efficacy is measured by the comparison of fractures in hip, vertebrae and limbs for those taking the drugs and those on placebo.

Pipeline products

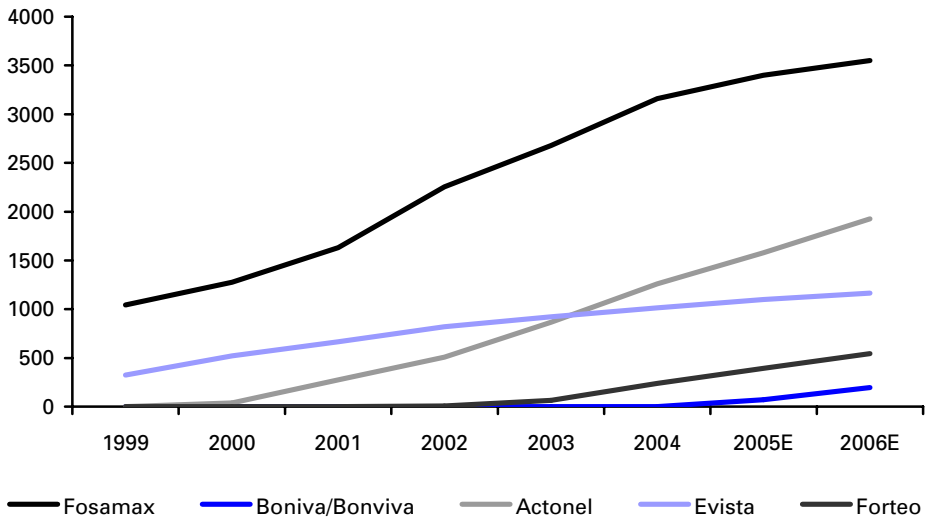
Currently, the osteoporosis development pipeline is primarily focused on new entrants in the existing bisphosphonate and SERM classes. As noted above, Roche/GSK's Boniva is a new bisphosphonate that recently won FDA approval as a once-monthly formulation. While the companies expect the less frequent dosing to prove a marketing advantage, we expect it may also bring its own challenges in terms of patient compliance. Separately, Pfizer and Wyeth are developing new SERMs which aim to improve on the efficacy and safety profile of Lilly's Evista. Pfizer's Oporia (lasofoxifene) was filed in late 2004, while Wyeth's bazedoxifene is slated for filing in 2005.

Figure 173: Key pipeline products for osteoporosis

Name	Sponsor	Class/Mechanism	Status	Est filing
Boniva	Roche/GSK	Bisphosphonate	Launch 2005	Approved
Oporia (lasofoxafine)	Pfizer	SERM	Launch 2005	Filed
bazedoxifene	Wyeth	SERM	Phase III	2006
Preos	NPS Pharmaceuticals	Parathyroid hormone	Phase III	2005
Aclasta	Novartis	Bisphosphonate	Phase III	2007
AMG 162	Amgen	Anti-RANKL mAb	Phase III	>2007
arzoxifene	Lilly	SERM	Phase III	>2007
AAE581	Novartis	Cathepsin K inhibitor	Phase II	>2007

Source: Deutsche Bank

Figure 174: Sales forecasts for key osteoporosis drugs ($ m)



Source: Company data, Deutsche Bank estimates

Figure 175: Sales forecasts for key osteoporosis drugs ($ m)

		1999	2000	2001	2002	2003	2004	2005E	2006E
Fosamax	Merck & Co	1045	1275	1630	2253	2677	3159	3400	3550
Boniva/Bonviva	Roche/GSK	0	0	0	0	0	0	73	196
Actonel	Sanofi-Aventis/P&G	0	40	277	508	866	1259	1580	1927
Evista	Eli Lilly	325	522	665	822	922	1013	1100	1165
Forteo	Eli Lilly	0	0	0	6	65	239	395	545

Source: Deutsche Bank

NOTES

Pain

- World market estimated at more than $17bn 2004
- Growth of NSAID category undermined by generic competition and, more recently, worldwide withdrawal of Vioxx (Merck)
- Treatment based on severity and acute vs. chronic nature of condition

Pain is one of the world's largest and most rapidly growing markets. Over 25 million people in the US suffer from acute pain related to injury or surgery and another 50 million experience chronic pain. The annual cost of pain management to the US economy is estimated at $100bn per year.

Physiology

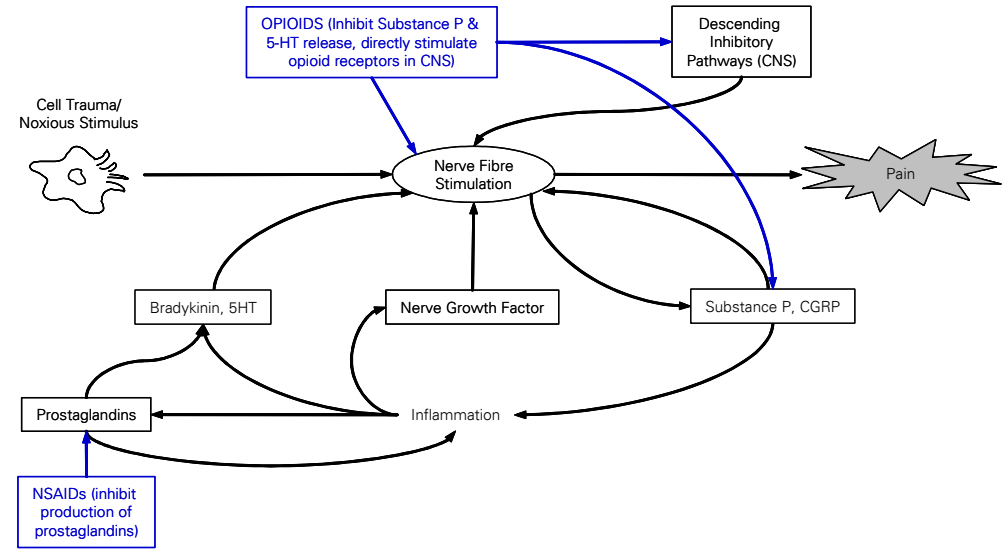
Pain is classified into several categories to help determine appropriate treatment. First, it is broadly characterised as acute or chronic. Acute pain is short lived, whereas chronic pain is usually described as persisting for more than three-to-six months. Chronic pain is further divided between somatogenic conditions, or those explicable by physiological causes, and psychogenic conditions, or those primarily associated with psychological origins. Finally, somatogenic pain may be either nociceptive, meaning that it is a result of normal activation of pain-sensitive nerve fibres, or neuropathic, resulting from nerve tissue damage.

In order to understand the mechanisms of pain, it is helpful to become familiar with the components of the nervous system. The nervous system is divided into two parts: the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS, which consists of the brain and spinal cord, communicates chemical signals to and from the PNS, which includes the sensory and motor nerve fibres throughout the body. Signals from the CNS tell the heart to beat faster or instruct a muscle to contract, while signals from the PNS inform the brain that a pinprick hurts.

Most painful sensations are a result of the nociceptive pathway. Following injury, damaged cells release several chemical mediators, including bradykinin, 5-hydroxytryptamine (5-HT) and histamine. Histamine primarily initiates an inflammatory response. Bradykinin and 5-HT stimulate nerve receptors, called nociceptors, which pass the signal from the PNS to the CNS, creating the painful sensation. Also, at the time of cell injury, arachidonic acid is released, which, with the help of the enzyme cyclooxygenase, produces prostaglandins. While not stimulating pain directly, these molecules enhance the pain-producing effects of bradykinin and 5-HT. They also contribute to the inflammatory response.

Many injuries also give rise to a hypersensitive state known as hyperalgesia, which causes a person to experience increased pain from a mild noxious stimulus. This phenomenon is responsible, for example, for a mild touch triggering pain when applied to sunburned skin. Hyperalgesia is caused by the release of two neurotransmitters, substance P and calcitonin gene-related peptide (CGRP), which sensitise the nerve fibres to future stimulation.

Figure 176: Physiological pathway of pain



Source: Rang, Dale, Ritter

Finally, neuropathic pain is caused by damage to the nerve fibres and can persist without any specific sensory nerve stimulation. It is generally linked to CNS disorders, such as stroke or multiple sclerosis, or conditions causing peripheral nerve damage, including diabetes, shingles or mechanical injury.

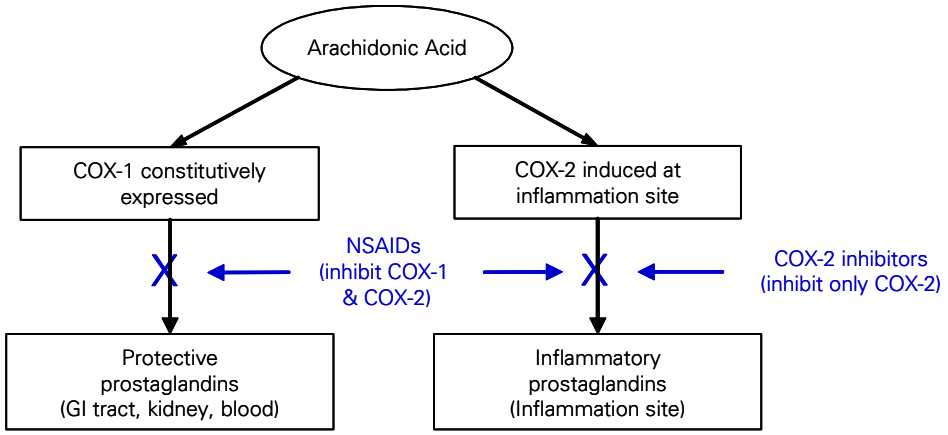
Pharmacological treatment

Given the complex causes and manifestations of pain, treatments vary widely and are best categorised into several groups based on the relevant conditions they aim to treat.

Mild-to-moderate pain (e.g. headache, arthritis). Low-level pain is generally treated with aspirin, acetaminophen or other non-steroidal anti-inflammatory drugs (NSAIDs). There are currently over 50 different NSAIDs on the market, most of which differ slightly in pharmacological characteristics or side effect profile but all of which (with the exception of acetaminophen) attempt to inhibit the inflammatory reaction. The NSAIDs' target is the cyclooxygenase (COX) enzyme, which is associated with the production of prostaglandins. Cyclooxygenase exists in two forms. The first of these, COX-1, exhibits protective effects and is constitutively expressed in most tissues, including the kidneys, gastrointestinal tract and blood platelets. Only the second form of the enzyme, COX-2, is involved in the inflammatory pathway.

Because most NSAIDs do not discriminate between these two enzymes, they disrupt the protective efforts of COX-1, leading to side effects such as gastrointestinal and kidney irritation. In an effort to avoid these complications, a new class of drug emerged that selectively targets the COX-2 enzyme. Although applicable in a number of pain indications, the COX-2 inhibitors have been most widely used for the treatment of osteoarthritis, a painful condition caused by erosion of cartilage and bone in the joints. Osteoarthritis is estimated to affect more than 50% of people over 65 and nearly all people over age 75.

Figure 177: COX-2 versus NSAID specificity


Arachidonic Acid
COX-1 constitutively expressed
COX-2 induced at inflammation site
NSAIDs (inhibit COX-1 & COX-2)
COX-2 inhibitors (inhibit only COX-2)
Protective prostaglandins (GI tract, kidney, blood)
Inflammatory prostaglandins (Inflammation site)

Source: Deutsche Bank

However, in late September 2004, the COX-2 class took a hit when Merck announced the worldwide withdrawal of its COX-2 inhibitor Vioxx, which was expected to see sales upward of $2.5bn for the full year. The withdrawal was based on data from a three-year trial designed to evaluate the use of Vioxx in preventing the recurrence of colorectal polyps. However, an interim analysis of the study revealed that after three years, patients receiving Vioxx had a two-fold greater risk of a cardiovascular event (e.g., stroke or heart attack) compared to those receiving placebo. (Note that while earlier data, including the 8,000-patient VIGOR study, had also suggested an increased cardiovascular risk associated with Vioxx, Merck previously argued that the difference was attributable to the cardioprotective benefit of the NSAID comparator, naproxen, rather than an adverse effect associated with Vioxx.)

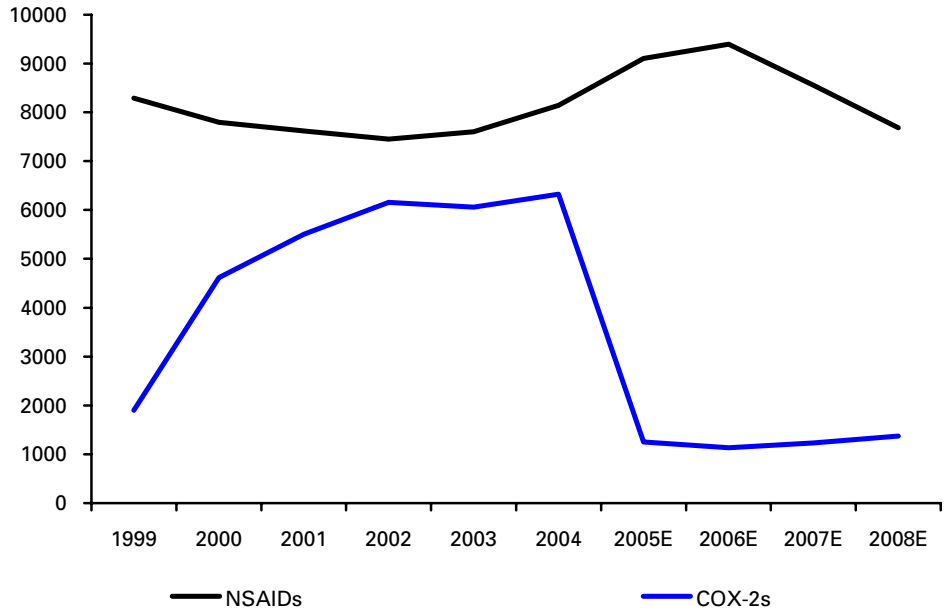
While it is unlikely to ever be known with certainty whether the Vioxx cardiovascular effect was drug-specific or class-related, its withdrawal, together with mixed safety data regarding other COX-2 players, suggests that this class will be permanently tainted. Indeed, following the Vioxx withdrawal, an FDA Advisory Committee decided that the cardiovascular risk was most likely a class effect and requested black box warnings for all members of the class. Although the FDA warning will in fact apply to *all* NSAIDs (including older non-selective products as well as the COX-2s), given that the combination of a traditional NSAID and a proton pump inhibitor (both of which are available generically) offers a similar GI profile to the COX-2s, we expect doctors will increasingly reserve use of COX-2s for only those patients at greatest risk of gastrointestinal side effects.

Figure 178: Leading COX-2 inhibitors and late-stage candidates

Brand	Generic	Company	Launch/Status	2004 sales
Celebrex	Celecoxib	Pfizer	1999	$3.3bn
Vioxx*	rofecoxib	Merck	1999	$1.5bn
Bextra**	valdecoxib	Pfizer	2001	$1.3bn
Arcoxia	etoricoxib	Merck	Approved ex-US only	$0.2bn
Dynastat	paracoxib (injectable)	Pfizer	Approved ex-US only	<$0.1bn
Prexige	lumiracoxib	Novartis	Filed	n.a.

*Source: Company data *Voluntarily withdrawn 30 September 2004 **Currently suspended by FDA. Pfizer in discussions about re-introduction.*

Figure 179: Sales growth of traditional NSAIDs vs. COX-2s ($ m)



Source: Wood Mackenzie

Figure 180: Sales growth of traditional NSAIDs vs. COX-2s ($ m)

	1999	2000	2001	2002	2003	2004	2005E	2006E	2007E	2008E
NSAIDs	8291	7795	7619	7450	7599	8140	9106	9392	8553	7683
COX-2s	1899	4616	5505	6155	6063	6322	1254	1138	1229	1374

Source: Wood Mackenzie

Severe pain (e.g. post-operative, cancer pain). In circumstances where NSAIDs are insufficient to alleviate pain, clinicians may turn to opioid drugs. 'Opioid' is a generic term for agents that stimulate so-called opioid receptors in the brain, triggering an analgesic effect. Opioids include both natural compounds, such as morphine and codeine, and synthetic derivatives such as meperidine, fentanyl and methadone. The pharmacological potency of each drug is related to its affinity for opiate receptors. However, morphine continues to serve as the standard for treatment and the benchmark against which other drugs are compared.

By acting directly on the CNS as well as peripherally via inhibition of 5-HT and substance P release, morphine is effective in most kinds of acute and chronic pain, with the exception of neuropathic pain. However, it is associated with significant side effects, including respiratory depression and severe constipation. (These effects may be alleviated by the administration of opioid antagonists, such as naloxone and naltrexone, which competitively bind to the same receptors as morphine.) Additional key concerns associated with opioids are their tolerance and dependence effects. Tolerance requires increased doses of the drug over time to produce an equivalent pharmacological effect. Dependence, on the other hand, induces physical withdrawal symptoms and/or psychological cravings for the drug after its use is discontinued. Due to these complications, morphine and its peers are not recommended for long-term use, except in severe cases, such as for the treatment of cancer pain.

Despite the enormous market for opioid drugs and the need for potent therapies without the tolerance and dependence characteristics of morphine, there is currently little of note in the pipeline. The only late-stage product relevant to this category is GlaxoSmithKline's alvimopan (licensed from Adolor), which is an opioid antagonist designed to treat post-operative ileus (loss of bowel control after surgery). However, given that the companies' Phase III

programme yielded equivocal results, we expect that the drug could struggle to win regulatory approval.

Neuropathic pain. Approximately 2-3 million Americans currently suffer from neuropathic pain, which is caused by injury to the peripheral or central nervous system. This includes a number of disorders, such as phantom limb pain, diabetic peripheral neuropathy (DPN), fibromyalgia and postherpetic neuralgia (PHN). Although apparently related to spontaneous activity of damaged sensory nerves, the exact mechanisms behind neuropathic pain are poorly understood.

Until recently, treatment generally relied on off-label use of anticonvulsants and antidepressants, including Pfizer's Neurontin (gabapentin). Neurontin, which may have earned as much as 50% of its historic sales from off-label use in pain management, gained official FDA approval in 2002 for use in PHN and DPN. More recently, Pfizer received FDA approval for Neurontin's successor, Lyrica, for both DPN and PHN, while Eli Lilly's new antidepressant Cymbalta won approval for DPN.

Figure 181: Selected development candidates for neuropathic pain

Name	Sponsor	Indication	Status	Est filing
Cymbalta	Lilly	DPN (fibromyalgia in Phase III)	Launch 2004	Approved
Lyrica	Pfizer	PHN, DPN	Launch 2005	Approved
ruboxistaurin	Lilly	DPN	Phase III	2005
lacosamide	Schwarz	DPN	Phase III	2006
milnacipran	Forest/Cyprus	Fibromyalgia	Phase III	2007

Source: Deutsche Bank

Clinical end-points

Clinical trial design varies according to the class of drugs. NSAIDs, including the COX-2s, must demonstrate pain relief equivalent to or better than that provided by gold-standard treatments such as naproxen or ibuprofen. However, in light of the Vioxx withdrawal discussed above, safety of any future COX-2 inhibitor will be paramount (and even then there is no guarantee that the regulators will feel comfortable approving another COX-2). The opioid-type and neuropathic pain drugs are evaluated for pain relief, primarily in comparison to morphine and placebo, respectively.

NOTES

Rheumatoid arthritis

- Rheumatoid arthritis affects an estimated 1-2% of the population
- Worldwide market for disease-modifying drugs worth over $6bn
- Key products include the TNF-α inhibitors, Enbrel, Remicade and Humira

Rheumatology refers to arthritis and over 100 other diseases of the joints, muscles and bones. Most significant among these is rheumatoid arthritis (RA), a chronic syndrome characterised by non-specific, usually symmetric inflammation of peripheral joints, resulting in progressive destruction of joint tissues. Approximately 1-2% of the population is affected by RA and one in three patients is likely to become severely disabled within 20 years. Onset of RA most often occurs between the ages of 25 and 50 and appears three times more often in women than in men.

Physiology

In healthy people, joints exist in places such as the hip, knee and finger, helping to protect the bones and facilitate mobility. Joints comprise several essential tissues: the joint capsule, which surrounds and supports the joint; the synovium, which lines the joint capsule and produces synovial fluid; synovial fluid, which lubricates and nourishes the joint cavity; and cartilage, which covers and cushions the ends of the bones.

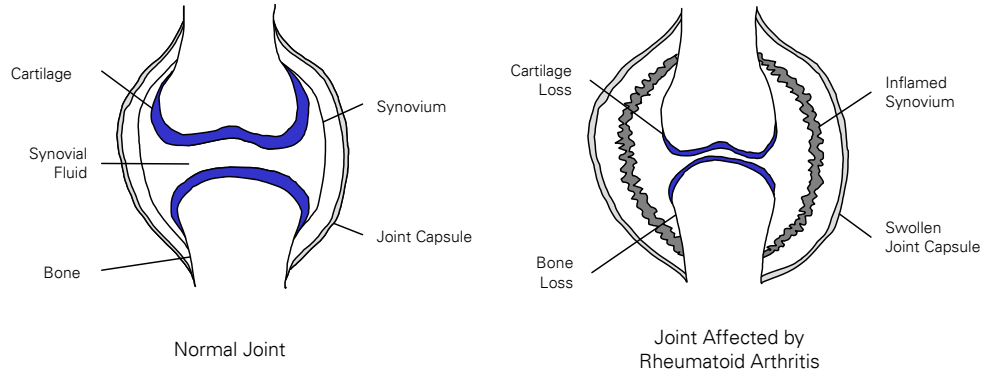
RA is a so-called autoimmune disease, a condition in which the body inappropriately directs a hostile immune response on its own tissues. In patients with RA, the body for unknown reasons attacks its own cells in the joint cavity. White blood cells, called leukocytes, are recruited to the synovium and cause inflammation. The typical symptoms of arthritis, including warmth, redness, swelling and pain, are a result of this inflammatory reaction. The inflammatory process also causes synovial cells to grow and divide abnormally, making the normally thin synovium unusually thick and puffy.

Eventually, as the abnormal synovial cells proliferate, they begin to destroy the protective cartilage and invade the bone itself. At the same time, the surrounding muscles and ligaments that support the joint system also become weak. In as little as one or two years after the onset of RA, bones begin to suffer permanent damage, thus warranting early diagnosis and treatment of the disease.

Pharmacological treatment

The initial focus of RA therapy is to treat the symptoms of the disease and maintain the patient's quality of life. In addition, the long-term goal of treatment is to halt disease progression and permanent deterioration of the joint tissues. While in early-stage patients physicians have traditionally focused on pain and inflammation relief, the treatment paradigm has begun to shift, with new emphasis being placed on the introduction of aggressive disease-modifying drugs from disease onset. The key groups of RA drugs are described below.

Figure 182: RA-induced inflammation of the joint



Source: National Institute of Arthritis and Musculoskeletal and Skin Diseases

- **NSAIDs:** NSAIDs are generally used as a first-line therapy for patients with mild RA. Relatively safe and inexpensive, they offer analgesic and anti-inflammatory properties that help to reduce the swelling and pain caused by RA.
- **Steroids:** Corticosteroids, which can be administered orally or via injection directly into the affected joint, offer the most potent short-term anti-inflammatory activity but also produce significant side effects, including hypertension, osteoporosis and increased susceptibility to infection. In particular, the clinical benefit of corticosteroids appears to diminish over time, which becomes problematic given the long-term nature of RA.
- **DMARDS:** Disease-modifying anti-rheumatic drugs (DMARDs) represent the second major category of RA drugs. Unlike the previously described drugs, which principally focus on short-term reduction of pain and inflammation, DMARDs attempt to halt the long-term progressive bone and joint damage. Methotrexate is the most commonly prescribed DMARD. It is an immunosuppressant, providing a more rapid onset of action and a slightly better side-effect profile than the other traditional DMARDs. In the event that methotrexate is not tolerated or is ineffective as a monotherapy, patients may also turn to other DMARDs, such as sulfasalazine, chloroquine and penicillamine.
- **Gold compounds:** Gold-containing compounds, such as auranofin (oral), aurothioglucose (injected) and aurothiomalate (injected), comprise a sub-category of DMARDs. Although not fully understood, these drugs appear to minimise the autoimmune response by interfering with lymphocyte proliferation. Additionally, auranofin appears to inhibit the induction of inflammatory cytokines, interleukin 1 (IL-1) and tumour necrosis factor α (TNF-α), both of which play an important role in normal inflammatory and immune responses. Once a primary second-line agent, the gold compounds have become less popular over time due to their modest efficacy, high side-effect profile and the availability of better alternatives.
- **Targeted therapies:** The cytokine-targeted drugs represent the most recent innovations in RA therapy. In fact, when Sanofi-Aventis launched Arava (leflunomide) in 1998, it was the first drug specifically approved for RA in over a decade.
  - **Arava** is a synthetic orally active drug that primarily exerts immunosuppressive activity via the interruption of pyrmidine synthesis, a key step required for T-cell proliferation. Similar in mechanism and side effects to methotrexate, it is used as a second-line agent in patients who have failed methotrexate therapy.
  - **Kineret,** launched in 2001, is a recombinant form of the naturally occurring IL-1 receptor antagonist (IL-1Ra). IL-1 is implicated in the inflammatory process and also appears to facilitate cartilage degradation. By binding to and inactivating IL-1, Kineret helps to reduce both inflammation and disease progression. However, Kineret's

efficacy has proven modest, and as a consequence, it is often reserved as a salvage therapy in TNF failures.

- **TNF-α inhibitors,** including Enbrel, Remicade and Humira. TNF-α is a cytokine that appears in elevated levels in the synovial fluid of RA patients and is implicated in RA-induced inflammation. Enbrel comprises a synthetic version of the TNF receptor, whereas Remicade and Humira are monoclonal antibodies that target TNF-α. Though all three drugs exhibit enhanced efficacy when used in combination with methotrexate, only Enbrel and Humira have the additional advantage of being approved as monotherapies and thus can be useful in the treatment of methotrexate-intolerant patients.

The launch of anti-TNFs has been a welcome advance in the treatment of RA. Although providing moderate benefit, methotrexate is disliked by patients, due to its significant and often intolerable side effects. These include nausea, vomiting, liver toxicity, chest pain, fatigue and many more. In comparison, the chief side effect of Enbrel, Remicade and Humira is injection site reaction, although the anti-TNFs also carry a black box warning about a small but important risk of serious infection.

Figure 183: Leading drugs for rheumatoid arthritis

Brand	Generic	Company	Launch	2004 sales
Enbrel	Etanercept	Amgen/Wyeth	1998	$2.6bn
Humira	Adalimumab	Abbott	2003	$0.8bn
Remicade	Infliximab	Johnson & Johnson	1999	$2.1bn
Arava	Leflunomide	Sanofi-Aventis	1998	$0.3bn
Kineret	Anakinra	Amgen	2001	<$0.1bn

Source: Company data

Clinical end-points

Clinical efficacy is generally evaluated using the American College of Rheumatology (ACR) response criteria, which measure improvements of 20% (ACR20), 50% (ACR50) and 70% (ACR70) from baseline. ACR20, for example, requires a 20% decrease in the number of tender and swollen joints, as well as improvements in three of the following five parameters: 1) patient's global assessment, 2) physician's global assessment, 3) patient's assessment of pain, 4) degree of disability and 5) level of acute-phase reactant.

Additional key considerations in clinical trial design include whether the drug is administered as a monotherapy or in combination with methotrexate, as this will define the label it later receives. In addition, trials for the newer drugs typically include safety end-points, so as to enable claims of superior side-effect profiles compared to methotrexate.

Figure 184: Comparison of TNF-α inhibitors in rheumatoid arthritis

	Enbrel (Amgen/Wyeth)	Remicade (J&J/SGP)	Humira (Abbott)	Cimzia (UCB)*
Dose	25 mg	3-10 mg/kg	40 mg	400 mg
ACR20 at 6months (control)	65% (58%)	50% (20%)	63% (30%)	60% (15%)
ACR50 (control)	40% (32%)	27% (5%)	39% (10%)	40% (0%)
ACR70 (control)	21% (14%)	8% (0%)	21% (3%)	29% (0%)
Sharpe score** (control)	0.57 (1.06)	0.5 (4.0)	0.1 (2.7)	n/a
Dosing	twice/week	once/8 weeks	once/2 weeks	once/4 weeks
Administration	Subcutaneous	Intravenous	Subcutaneous	Subcutaneous
Approved as monotherapy?	Yes	No	Yes	Expected
Side Effects	Injection site reaction	Infusion reaction, uRTI, rash, sinusitis, headache, cough	Injection site reaction, rash, back pain, uRTI, sinusitis	Injection site reaction, uRTI
Black Box Warning	Risk of serious infections and sepsis (May 99)	Risk of infection including tuberculosis and invasive fungal infections	risk of infection including tuberculosis	Expected

*Source: Company data *In Phase III; data from 12 week Phase II study. **Sharpe score measures change in structural joint damage assess by x-ray, smaller number indicates less damage.*

Pipeline products

Given the favourable convenience, cost and efficacy profile of methotrexate, most new RA drugs in development are targeted at methotrexate failures. However, with increasing acceptance of the anti-TNFs, certain development products such as Roche's Mabthera/Rituxan, are first being tested in TNF-failures before being moved forward in the treatment paradigm.

The most advanced pipeline candidate is Bristol-Myers' abatacept, which was filed in the US and Europe in late 2004. Twelve-month Phase III data presented in October 2004 confirmed that the drug offers a competitive profile relative to the anti-TNFs but abatacept appears to be slower acting with six-month data suggesting a more modest benefit relative to the anti-TNFs at a similar time point. One of the key advantages of abatacept, however, is likely to be its safety profile and the fact that it does not carry the same risk of serious infections seen with the TNF inhibitors.

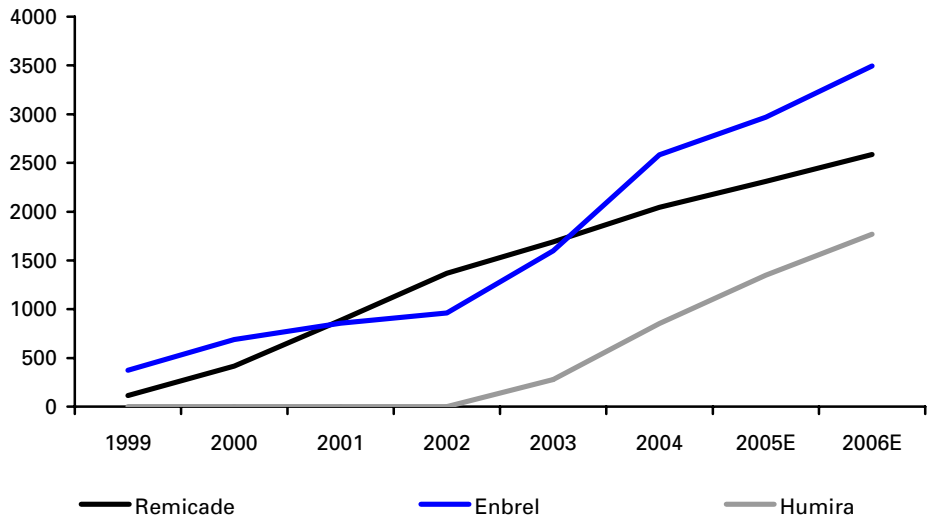
Also of note in development is UCB's Cimzia (formerly CDP870), a new entrant in the anti-TNF class that hopes to provide competitive efficacy together with less frequent dosing (once every four weeks) and a lower cost of manufacturing. Elsewhere, Roche is testing its non-Hodgkin's lymphoma agent MabThera in RA, with Phase II data suggesting that two initial doses of the drug can confer benefit for a full 48 weeks. Roche also has a second drug, tociluzumab (originated by Chugai), in Phase III development with preliminary data suggesting a promising efficacy profile. However, neither of the Roche drugs appears to have a clean side effect profile, thus potentially limiting their potential in this indication.

Figure 185: Key pipeline products

Name	Sponsor	Mechanism	Status	Est filing
Orencia (abatacept)	Bristol-Myers Squibb	T-cell co-stimulation blocker	Launch 2005	Filed
Cimzia (CDP870)	UCB	Anti-TNF mAb	Phase III	2007
MabThera	Roche/Genentech	B-cell modulator	Phase III	2005/7*
tocilizumab (MRA)	Roche/Chugai	Anti-IL-6 mAb	Phase II	2007
CNTO 148	Johnson & Johnson	Anti-TNF mAb	Phase II	>2007
TACI-Ig	Serono	Inhibits B-cell stimulation	Phase II	>2007
274150	GlaxoSmithKline	iNOS inhibitor	Phase II	>2007
AMG714	Amgen/Genmab	Anti-IL-15 mAb	Phase II	>2007
temsirolimus	Wyeth	mTOR inhibitor	Phase II	>2007

*Source: Company data *Initial filing in anti-TNF failures (2005) followed by secondary filing in MTX failures (2007)*

Figure 186: Sales growth for TNF-alpha inhibitors ($ m)



Source: Company data, Deutsche Bank estimates

Figure 187: Sales growth for TNF-alpha inhibitors ($ m)

		1999	2000	2001	2002	2003	2004	2005E	2006E
Remicade	J&J/Schering-Plough	115	418	887	1369	1690	2043	2310	2586
Enbrel	Amgen/Wyeth	375	690	856	961	1599	2581	2971	3495
Humira	Abbott Laboratories	0	0	0	0	280	852	1350	1770

Source: Company data, Deutsche Bank estimates

NOTES

Transplantation and Immunosuppression

- World market worth approximately $3.7bn in 2004
- Growth primarily constrained by availability of organs for transplant
- Key players are Novartis and Roche

More than 20,000 solid organ transplants and 40,000 bone marrow transplants are performed annually worldwide. Tens of thousands more patients remain on transplant waiting lists. With viable donor organs far outnumbered by patients in need, the success of each transplant procedure is critical. Primarily, this requires effective immunosuppressive drugs to minimise the risk of rejection.

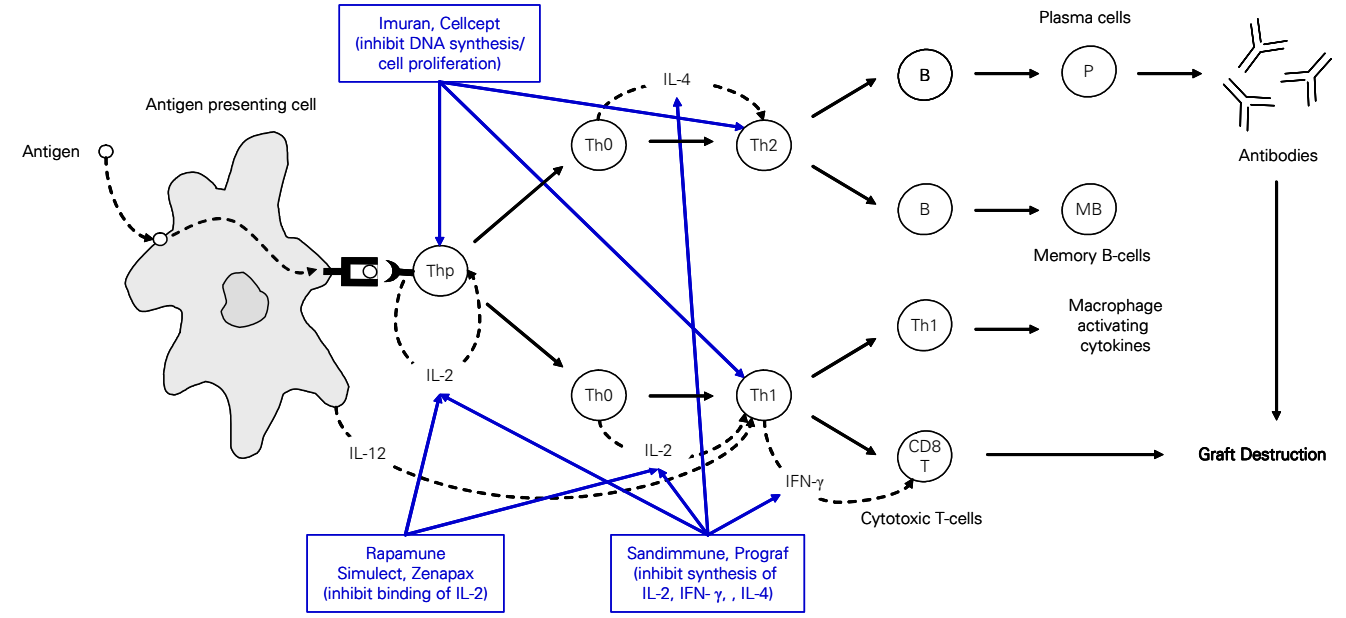
The likelihood of rejection is automatically reduced when patients receive grafts of an identical genetic nature via an autograft (use of the patient's own tissue) or an isograft (a transfer between identical twins). However, most transplants utilise allogenic (genetically dissimilar) tissues. Because the body is conditioned to attack cells that it recognises as foreign, its innate response is to reject the unfamiliar tissue. To address this issue, transplant patients are treated with strong doses of immunosuppressive drugs.

Physiology

The transplant rejection process is a result of the body's natural protective immune response. Usually, when a pathogen such as a bacterium or virus enters the body, it exhibits on its cell surface antigens that the immune system recognises as foreign. Upon recognition, these antigens are taken up by certain cells, called antigen-presenting cells (APCs), which process the antigen and display it on their cell surface to uncommitted T-helper cells (Thp). When the naïve T-helper cells see the antigen, they replicate and become activated T-cells (T0). T0 cells subsequently proliferate into Th1 or Th2 cells, depending on the particular cytokines present. In the Th1 or "cell-mediated" pathway, T0 cells give rise to an army of cytotoxic CD8 T-cells capable of finding and killing infected cells. The Th2 pathway, often called the 'humoral' response, gives rise to antibody-producing B-cells. Certain B-cells also become memory cells, which as the name suggests, remember the foreign antigen, thus enabling an immediate and potent response upon its reappearance.

Both of these pathways may lead to the rejection of transplanted allografts. When tissue from a genetically different donor is transplanted, antigens expressed on the cells of the donor's tissue trigger an immune reaction. Acute rejection is principally associated with the cell-mediated response. Late graft deterioration is thought to be caused by gradual antibody-mediated damage. In addition, some patients may experience hyperacute rejection. This reaction occurs when a patient has been previously exposed (for example, via pregnancy, blood transfusion or transplant) to cells expressing antigens identical to those on the graft. Because memory cells recall the foreign antigens, they immediately launch an attack on the new tissue.

Figure 188: Mechanism of graft rejection



Source: Deutsche Bank, Rang, Dale & Ritter

Pharmacological treatment

To reduce the likelihood of rejection, donor tissues are tested prior to transplant to determine which antigens they express. By comparing their genetic makeup, donor and recipient may be matched so as to minimise antigenic differences. Because of residual responses not resolved via antigen-typing, a course of immunosuppressive drugs is also essential to the transplantation process. Given in high doses at the time of transplant, these drugs generally suppress all immune responses, making infection the leading cause of death in transplant recipients. In addition, although drug doses may be lowered over time, immunosuppressive therapy can rarely ever be stopped completely.

Historically, immunosuppression has largely relied on a triple-drug cocktail comprising Sandimmun/Neoral, azathioprine and a corticosteroid. Although newer agents have emerged that may be used as substitutes for Sandimmun and azathioprine, reliance on a three-pronged approach persists. This triple cocktail is also the same across different types of transplant procedures, with the exception of bone-marrow transplants, where methotrexate is used in place of azathioprine. Although all drugs aim to suppress the immune system in some capacity, they each act by different pathways as described below:

- **DNA synthesis inhibitors.** Azathioprine and Cellcept (mycophenolate) both suppress the immune response by interfering with the synthesis of DNA, a critical step required for cell division and proliferation. Azathioprine was first used in transplantation in the 1960s. Unfortunately, azathioprine acts as an anti-metabolite, thus indiscriminately depleting bone marrow as well. Cellcept was introduced in 1995 as a more selective alternative to azathioprine. While utilising the same underlying mechanism, Cellcept blocks a particular enzyme called IMPDH that is only required for DNA synthesis in lymphocytes (T-cells and B-cells). Other cells that can employ an alternative "salvage" pathway are spared.

Figure 189: Standard post-transplant drug regimens

Solid organ transplant	Bone marrow transplant
Sandimmun or Prograf	Sandimmun or Prograf
+	+
azathioprine or Cellcept	methylprednisolone
+	+
prednisone or methylprednisolone	methotrexate

Source: Deutsche Bank

- **Calcineurin inhibitors.** These drugs inhibit immune cell replication by interrupting the synthesis of certain cytokines responsible for stimulating cell proliferation. Sandimmun and Neoral (cyclosporin) bind to and inactivate calcineurin, an intracellular intermediary required in the cytokine synthesis process. However, because production is downregulated but not entirely eliminated, affected cells preserve some ability to react against infectious agents. Prograf (tacrolimus) acts by a similar mechanism but has demonstrated somewhat more favourable efficacy.
- **Corticosteroids.** Corticosteroids play a role in the treatment of many diseases but it is their immunosuppressive capability that makes them useful in transplantation. These drugs – typically prednisone or methylprednisolone – significantly reduce overall lymphocyte and monocyte counts by directing them out of the circulating blood into other non-circulating compartments.
- **Cytokine inhibitors.** Rather than affecting the initial synthesis of cytokines, two recently introduced monoclonal antibodies, Simulect (basiliximab) and Zenapax (daclizumab), block their cellular function. By interfering with the binding of the cytokine IL-2, they intercept the message telling activated T-cells to proliferate. A third drug in this category, Rapamune (sirolimus) also interferes with cytokine stimulation, albeit through a different mechanism. Being fairly new, all of these drugs are primarily used as additive agents and none are FDA approved for procedures other than kidney transplants.
- **Anti-lymphocyte agents.** Orthoclone (OKT3) is a monoclonal antibody that reacts with the CD3 receptor complex on T-cells, rendering the cells immuno-incompetent. Because of its toxic effects and the risk of oversuppression, Orthoclone is generally not used at the time of transplant but rather in the event of acute rejection. Also in this category are the polyclonal antibodies, Thymoglobulin and Atgam (antithymocyte globulin), which are most often used as adjuncts, enabling the administration of other immunosuppressive drugs at lower, less toxic doses.

Figure 190: Leading immunosuppressive drugs

Brand	Generic	Manufacturer	2004 sales
Cellcept	Mycophenolate	Roche	$1.1bn
Sandimmun/Neoral	Cyclosporine	Novartis	$1.0bn
Prograf	Tacrolimus	Fujisawa	$1.1bn
Simulect	Basiliximab	Novartis	<$0.1bn
Zenapax	Daclizumab	Roche	<$0.1bn
Rapamune	Sirolimus	Wyeth	$0.3bn

**Assumes Pfizer merger with Pharmacia*
Source: Company data

Clinical end-points

Key clinical end-points in transplantation trials are patient survival, graft survival and incidence of acute rejections. These measures are generally followed for a period of six-to-twelve months. Because of the severe penalty for ineffective drugs (i.e., graft rejection), preclinical and early clinical safety and efficacy data for novel immunosuppressants are subject to heightened scrutiny. Once in later stage trials, the drugs are used as incremental agents, given in addition to a traditional cocktail comprising azathioprine, Sandimmun and/or corticosteroids.

Pipeline products

Most of the drugs currently in development attempt to offer more selective methods of immunosuppression. The most developed of these candidates is Novartis' Certican, which has been deemed 'approvable' by the FDA and acts on the same intracellular receptor as Rapamune. More interesting is Novartis' FTY720 which employs a unique lymphocyte-homing mechanism to direct cells away from the graft, while preserving their ability to respond to other immune challenges. However, after an intial Phase III trail failed to meet its non-inferiority endpoint and certain side effects were seen more frequently in the FTY720 arm, the future of this drug in transplant is increasingly dubious. Separately, Bristol-Myers is developing belatacept (LEA29Y), which is a re-engineered version of its rheumatoid arthritis drug Orencia (abatacept). By selectively binding to antigen presenting cells, belatacept aims to inhibit immune system stimulation. In addition, because belatacept does not have the same broad spectrum activity and interactions of the calcineurin inhibitors, it may offer an enhanced safety profile.

Figure 191: Key pipeline products

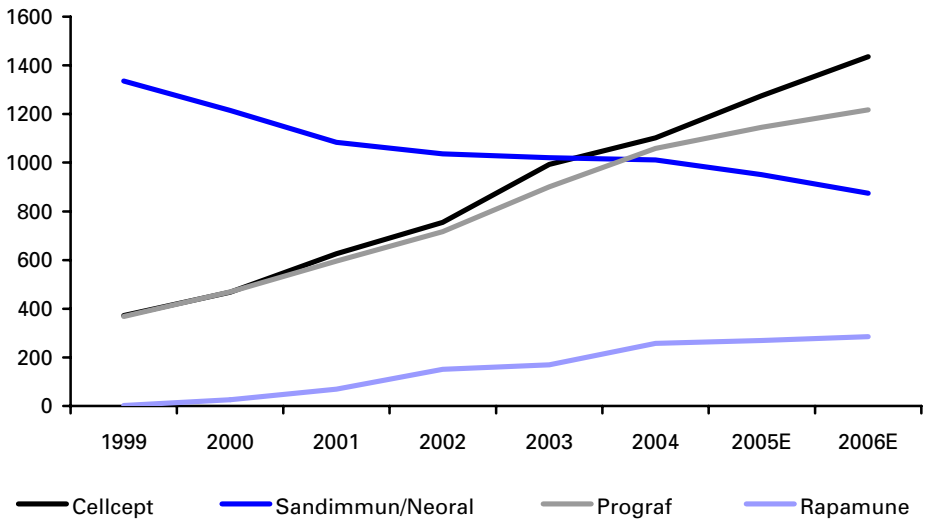
Name	Sponsor	Class/Mechanism	Status	Est filing
Certican	Novartis	Rapamycin analogue	"Approvable"	Filed
belatacept(LEA29Y)	Bristol-Myers Squibb	T-cell co-stimulation blocker	Phase III	2007
FTY720	Novartis	S1P-R agonist	Phase III	TBD

Source: Deutsche Bank

One of the challenges that faces all of these new products is physicians' reluctance to switch patients from one immunosuppressive protocol to another. In fact, this reluctance extends to switches from branded products to generic equivalents and is responsible for the ongoing sales of drugs such as Neoral that lost their patent protection years ago. Thus, the hurdle for new drugs to gain acceptance is higher on average for transplantation than for other therapeutic areas.

Also limiting the growth of this sector is the shortage of organs available for transplant. This is a growing area of focus for both medical researchers and drug companies. In particular, living donor transplants are becoming increasingly common for recipients requiring a kidney, and even in some cases, for those requiring a liver or lung transplant. Pharmaceutical companies are also exploring the viability of xenotransplantation, or the transplantation of non-human (usually "porcine" or pig) tissues. While clinical use of xenografts is still a long way off, a significant stride was made with PPL Therapeutics' successful breeding of pigs that lack the enzyme responsible for adding a certain sugar molecule to the surface of pig cells. Because the pig sugar molecule normally causes hyperacute rejection of the transplanted organ within minutes, the ability to delete the gene responsible for producing the enzyme represents a critical step toward the creation of porcine tissues that can be transplanted in humans.

Figure 192: Sales growth of key immunosuppressants ($ m)



Source: Company data, Deutsche Bank estimates

Figure 193: Sales growth of key immunosuppressants ($ m)

		1999	2000	2001	2002	2003	2004	2005E	2006E
Cellcept	Roche	372	468	626	754	993	1101	1275	1436
Sandimmun/Neoral	Novartis	1336	1215	1084	1036	1020	1011	950	874
Prograf	Fujisawa	369	469	596	717	901	1059	1145	1217
Rapamune	Wyeth	3	26	70	151	170	258	270	285

Source: Deutsche Bank

NOTES

Multiple sclerosis

- Worldwide market worth roughly $4.4bn in 2004
- Growth estimated at 20%
- Market dominated by interferons, including Biogen IDEC's Avonex and Serono's Rebif

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS) that affects approximately 300,000 people in the US and 350,000 in Europe. It is most often diagnosed in adults between the ages of 25 and 40 and affects twice as many women as men. While the exact cause of MS remains a mystery, epidemiology studies imply both a genetic and an environmental component to the disease.

The progressive symptoms of MS typically include blurred vision, muscle weakness and lack of coordination. Some patients also experience cognitive impairment such as difficulty with concentration, memory or judgement. Based on the frequency and resolution of these symptoms, MS patients are classified into four primary categories listed below.

Figure 194: Multiple sclerosis patient classification

Type	Incidence	Characteristics
Relapsing-remitting (RRMS)	40%	Abrupt onset of a few attacks, followed by partial or total remission
Secondary progressive (SPMS)	40%	Few attacks per year, with progressive deterioration in condition and physical ability
Primary progressive (PPMS)	10%	Rapid deterioration from onset, with only brief periods of improvement or stabilization
Benign	10%	Abrupt onset of a few attacks, followed by stabilization and no permanent disability

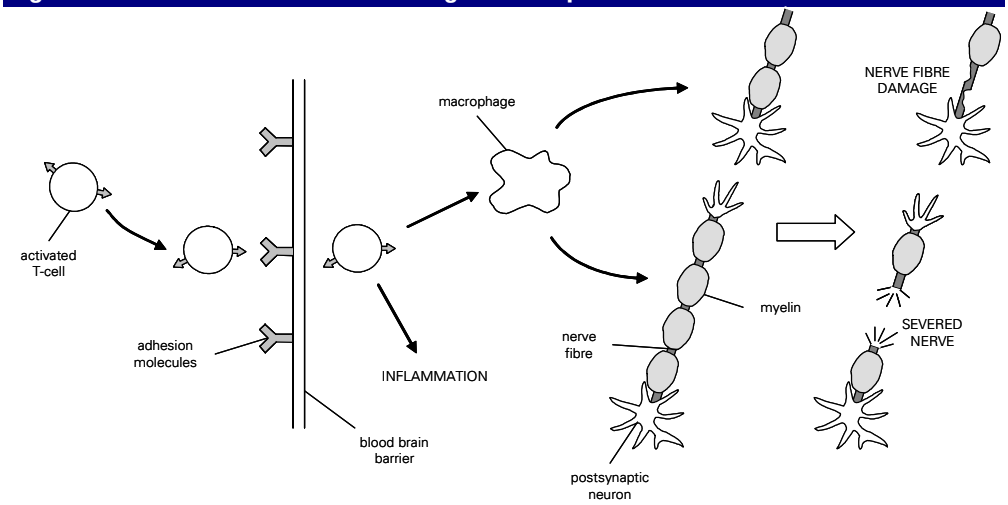
Source: Deutsche Bank

Physiology

MS is caused when immune system cells attack the myelin sheath that surrounds nerve fibres in the brain and spinal cord. In addition to its protective role, myelin normally facilitates the smooth, high-speed transmission of chemical messages between the brain, the spinal cord and the rest of the body. Damage to the myelin sheath and the underlying neuron, coupled with an inflammatory response, leads to formation of lesions or "plaques" and impairment of the nerves' ability to conduct messages. In the case of minor damage, the myelin may be able to repair itself and restore normal functionality. However, as the disease progresses, the damage often becomes irreparable.

On a cellular level, MS damage results from several malfunctions in the immune system as shown in Figure 195. First, certain immune system cells, known as T-cells, become activated and primed to attack the body's own myelin tissues. Second, the blood-brain barrier, which usually prevents large molecules from passing from the bloodstream into the CNS, becomes permeable to the activated T-cells. This occurs due to overexpression of so-called "adhesion molecules" that line the blood vessels and can shepherd molecules across the blood-brain barrier. Once inside the CNS, the activated T-cells recruit macrophages and initiate an inflammatory response. It is these macrophages that are primarily responsible for the myelin destruction and nerve damage.

Figure 195: Mechanism of nerve damage in multiple sclerosis



Source: Deutsche Bank

Pharmacological treatment

As no known cure for MS exists, treatment focuses on drugs designed to reduce the severity and frequency of attacks. Acute exacerbations are usually treated with short-term, powerful steroids or muscle relaxants, whereas prevention of relapses and progressive nerve damage has traditionally relied on the interferons. The exact mechanism by which the interferons slow disease progression is unknown, but there is evidence suggesting they may downregulate certain inflammatory cytokines, inhibit T-cell proliferation and/or reduce blood-brain barrier permeability and T-cell migration into the CNS. There are currently three interferons on the market: Betaseron (interferon β-1b), Avonex (interferon β-1a) and Rebif (interferon β-1a). Avonex and Rebif are generally used as primary therapies, while Betaseron is reserved as a second-line agent. A fourth non-interferon agent, Copaxone, has also been available for some time but is generally reserved for patients who fail interferon therapy.

The relative efficacy of the interferons – particularly Avonex and Rebif, which contain the same active ingredient – has been debated, prompting Serono to conduct its 48-week head-to-head EVIDENCE study, which compared Rebif and Avonex in patients with RRMS. The findings of this study (see Figure 196) formed the basis of Serono's successful motion to overturn Avonex' orphan drug status in the US (originally due to expire in 2003) and allow for the early launch of Rebif.

Figure 196: EVIDENCE study results

	Rebif	Avonex
	44 μg, 3x/week	**30μg, 1x/week**
Number of patients	339	338
Proportion relapse-free at 48 weeks	62%	52%
Mean number of MRI T2 active lesions at 48 weeks	0.9	1.4
Proportion with no T2 active lesions	63%	45%
Side effects		
– Injection site reaction	83%	28%
– Liver function disorder	18%	9%
– Change in white blood cell counts	11%	5%

Source: Serono

In late 2004, the FDA approved Elan/Biogen IDEC's Tysabri, a novel monocloncal antibody which is the first in an entirely new class of drug to treat MS. Tysabri binds to α4 integrin, a receptor present on T-cells that facilitates migration across the blood-brain barrier, and thereby inhibits T-cell trafficking into the CNS and destruction of myelin tissues. Based on one-year clinical data that suggested a significant improvement over the interferons, the FDA allowed an accelerated regulatory filing and approved the drug in November 2004. However, less than four months after launch, Tysabri suffered a major setback when three patients were diagnosed with a rare and frequently fatal condition known as progressive multifocal leukoencephalopathy (PML). This led Elan and Biogen to withdraw the drug from the market, although they companies hope for an eventual return as they gain a greater understanding as to the cause of the PML cases.

Figure 197: Comparison of leading multiple sclerosis drugs

	Avonex	Rebif	Betaseron	Tysabri
Generic	interferon β-1a	interferon β-1a	interferon β-1b	natalizumab
Company	Biogen	Serono	Schering	Elan/Biogen IDEC
Launch (USA/Europe)	1996/1997	2002/1998	1993/1996	2004
Approved indications	RRMS	RRMS	RRMS, PPMS (Europe only)	RRMS
Route of delivery	intramuscular	Subcutaneous	subcutaneous	intravenous
Dose	30 µg	22 or 44 µg	250 µg	300mg
Dosing frequency	1x/week	3x/week	3x/week	1x/4 weeks
% reduction in exacerbations vs. placebo at two years	-18%	-32%	-31%	-67%
% patients exacerbation free (placebo) at two years	38% (26%)	32% (15%)	25% (16%)	67% (41%)

Source: Company data

Clinical end-points

The severity of MS-induced disability is most often evaluated via the expanded disability status scale (EDSS), a ten-point scale divided into half-point increments. Unfortunately, this scale (as well as many others that have tried to improve upon it) comes in for much criticism, due to its high subjectivity, non-linearity and low test-retest reliability. Given these deficiencies, most investigators employ as primary end-points more objective measures, including relapse rates and the number of MS lesions visible via magnetic resonance imaging (MRI) scans.

It is also worth noting that with substantial evidence supporting the long-term efficacy of the interferon drugs, clinical evaluation may begin to rely on head-to-head studies rather than traditional placebo-controlled trials. If this emerges as the standard in the future, it may represent a greater challenge for new drugs seeking approval.

Pipeline products

MS has traditionally been a very risky area for product development, with a number of drug candidates having failed in late-stage trials, and most recently Tysabri being withdrawn due to side effect risks. Other once-promising compounds such as Linomide, LeukArrest and Schering's CCR1 antagonist also failed in Phase II or III due to lack of efficacy and/or due to significant side effects.

While the launch of Tysabri represented (at least temporarily) a significant step forward in terms of efficacy, the focus of the MS pipeline is now on the development of an orally delivered (versus injectable) product. In particular, Serono and IVAX are developing Mylinax, which contains the active ingredient cladribine, an older drug currently marketed as a high-dose intravenous formulation for the treatment of certain leukaemias. Initial clinical studies of

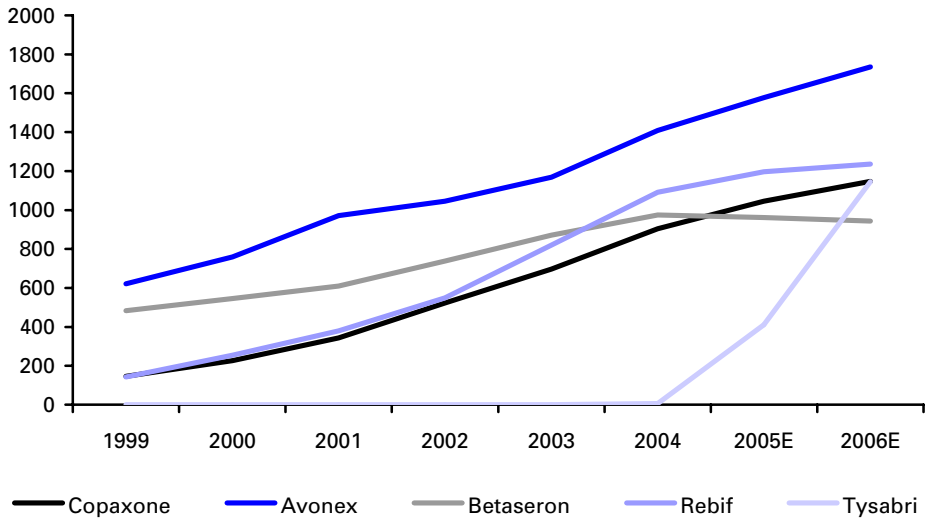
intravenous cladribine demonstrated efficacy in MS and the companies began a Phase III trial of the oral formulation in early 2005. Separately, Novartis is developing its transplant drug FTY720 in multiple sclerosis. Phase II studies showed a 55% reduction in relapse rate and Phase III trials are slated to begin in late 2005. However, as companies must typically run two-year Phase III programmes in this indication, approval of any of the oral candidates is unlikely before 2008/9.

Figure 198: Key pipeline products for multiple sclerosis

Name	Sponsor	Class/Mechanism	Status
teriflunomide	Sanofi-Aventis	Pyrimidine synthesis inhibitor	Phase III
Mylinax (cladribine)	Serono/IVAX	Purine analogue	Phase III
FTY720	Novartis	S1P-R agonist	Phase II
683699	GSK/Tanabe	α4 integrin antagonist	Phase II
laquinimod	Teva	Immunomodulator	Phase II
ABT 874	Abbott/CAT	Anti-IL-12 mAb	Phase II
E2007	Eisai	AMPA receptor antagonist	Phase II

Source: Deutsche Bank

Figure 199: Sales growth of leading multiple sclerosis drugs ($ m)



Source: Company data, Deutsche Bank estimates

Figure 200: Sales growth of leading multiple sclerosis drugs ($ m)

		1999	2000	2001	2002	2003	2004	2005E	2006E
Copaxone	Aventis	147	228	343	522	697	903	1046	1147
Avonex	Biogen	621	760	971	1045	1169	1408	1577	1735
Betaseron	Schering	483	546	610	738	870	974	962	943
Rebif	Serono	143	254	380	549	819	1091	1196	1236
Tysabri	Elan/Biogen IDEC	0	0	0	0	0	6	410	1146

Source: Deutsche Bank

Antibiotics

- World market in 2004 worth around $25bn
- Value growth flat due to the impact of patent expiries
- Resistance an increasing feature and driving development
- Leading companies include GSK, Pfizer, Roche and Daiichi

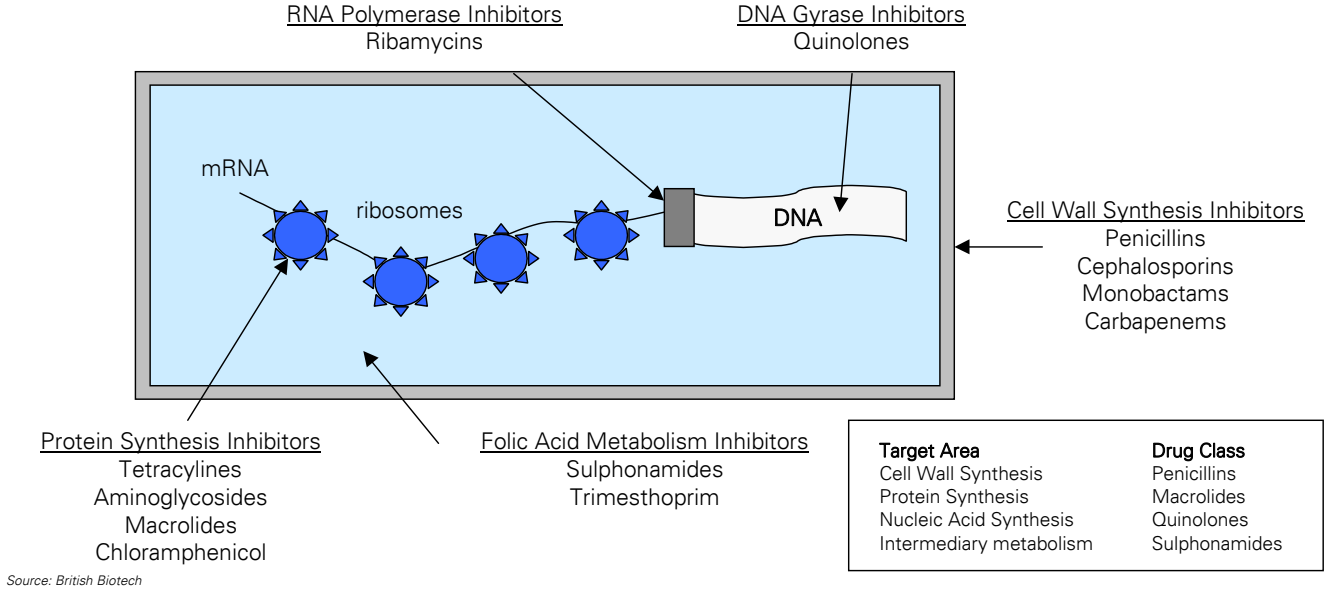
Antibiotics are used to kill the bacteria responsible for many infections. First developed commercially in the late 1940s following Alexander Fleming's discovery of penicillin in 1928, they have played a major role in the development of today's pharmaceutical industry. Antibiotics form a major class of drugs - it is estimated that they account for sales of roughly $25bn, equivalent to nearly 6% of the sales of the entire pharmaceutical industry.

Bacterial infections are a growing problem. In recent years, rising resistance to existing treatments has led to renewed interest from research-based pharmaceutical companies into the development of new and effective products.

Physiology

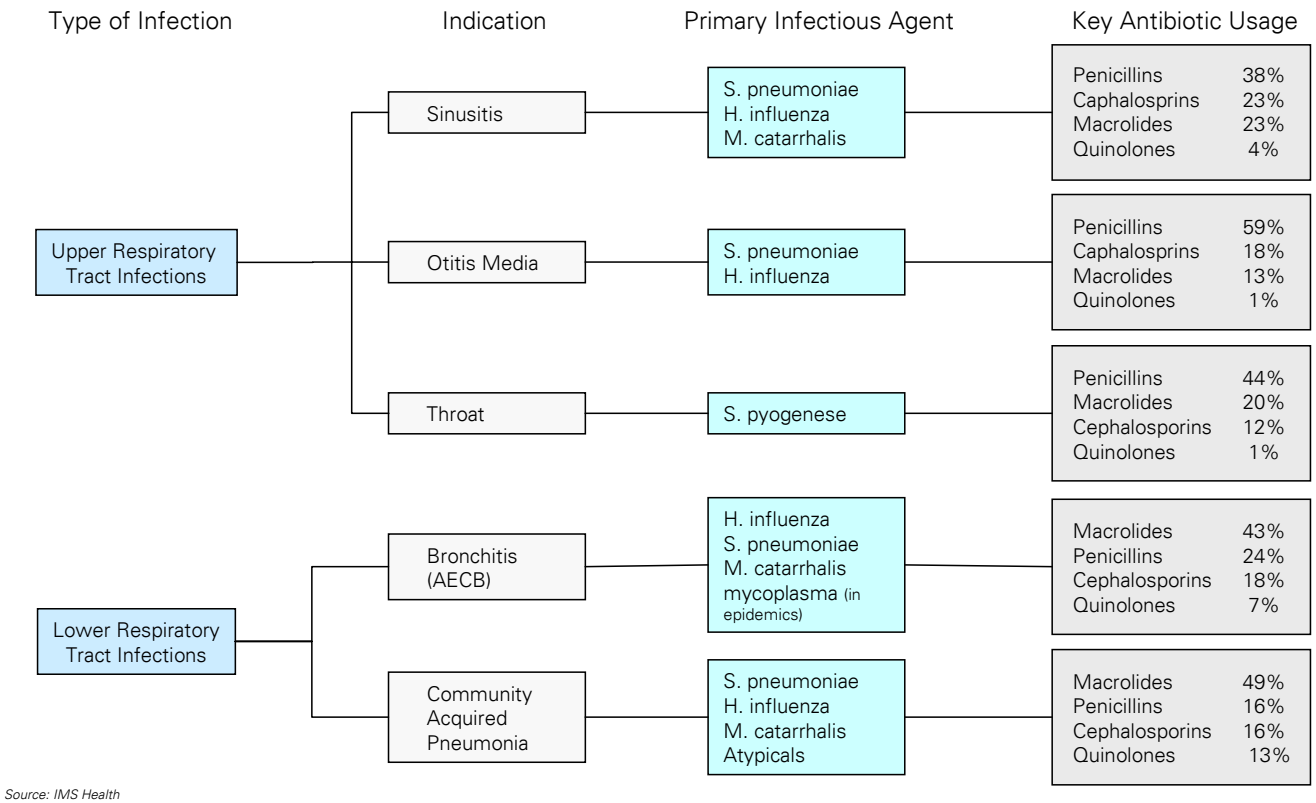
Antibiotics work by interfering with specific and essential processes within the bacterial cell. In essence, their development has centred on manipulating mechanisms and pathways that are vital to the bacteria's replication, yet which are either not found in humans or differ significantly. This limits, but does not eliminate, the drugs' toxicity to humans.

Figure 201: Antibiotics and bacteria - points of action



Source: British Biotech

Figure 202: Antibiotics – Respiratory tract infections and antibiotic usage



Source: IMS Health

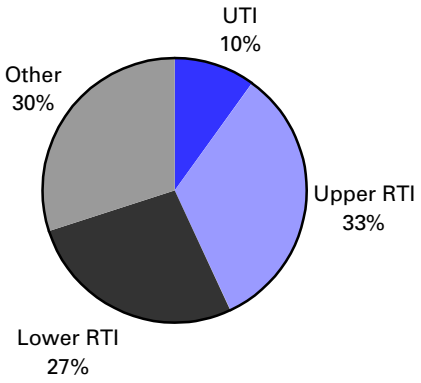
There are several different classes of bacteria, of which the four most significant are the penicillins, cephalosporins, macrolides and quinolones. Several of these target the same key metabolic process in a bacterium, albeit in a different way. As illustrated in Figure 201, the main areas of interference tend to be cell wall synthesis (for example, penicillin, cephalosporin), protein synthesis (for example, macrolides and tetracyclines), nucleic acid synthesis (quinolones) and essential intermediate pathways (for example, sulphonamides).

Bacteria are typically classed as either Gram-positive or Gram-negative. The 'Gram' definition reflects the difference in structure of the bacterial cell wall and, consequently, whether they are stained with dye in a Gram test. Gram-positive bacteria tend to be associated with respiratory tract infections (RTI), while Gram-negative bacteria are associated with infections of the urinary tract (UTI). Note that almost 60% of bacterial infections are in the respiratory tract, with only 10% in the urinary tract. Respiratory tract infections (RTIs) may be further broken down into those affecting the upper and lower regions.

Pharmacological treatment

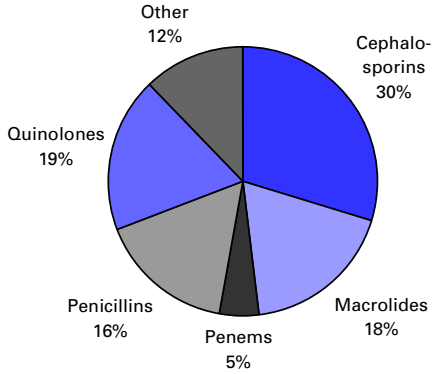
Given the variety of options, choice of treatment typically depends on several factors, not least the nature of the infection (e.g., RTI or UTI), patient history (allergic reaction to penicillin is quite common), potential drug interactions and so on. Increasingly, attention is also being given to resistance, which has become a major problem. Drug usage may also be limited by the form in which the antibiotic is administered (i.e. whether it is taken orally or injected). Use of injectable antibiotics is typically limited to hospitals (a feature that generally implies more modest sales potential). The four main classes (excluding the smallest class of carbapenems, which accounts for just 5% of antibiotic sales) are described in Figure 205.

Figure 203: Antibiotic sales by infection (2004)



Source: Deutsche Bank

Figure 204: Antibiotic sales by type (2004)



Source: Wood Mackenzie

Figure 205: Main antibiotic classes – summary characteristics

Class	Penicillins	Cephalosporins	Macrolides	Quinolones
Class value 2004	$4.2bn	$7.6bn	$4.6bn	$4.7bn
Sales growth rate (2004-08E)	-4%	-4%	+1%	0%
RTI/UTI	Mainly uRTI	Mainly uRTI	Mainly lRTI	Mainly UTI/new RTI
Key product	amoxycillin	ceftriaxone	azithromycin	levofloxacin
Lead Brand	Augmentin	Rocephin	Zithromax	Levaquin
Action point	Cell wall (B lactam)	Cell wall (B lactam)	Protein synthesis	DNA coiling
Side effects	Allergic reaction	Allergic reaction	GI disturbance	GI, headaches
Administration	Mainly oral	Mainly injected	Mainly oral	Mainly oral

Source: Deutsche Bank, Wood Mackenzie

Penicillins: Penicillin was the first modern antibiotic and is one of the group of beta-lactams, which includes cephalosporins and carbapenems (among others). It acts by interfering with the synthesis of bacterial cell walls. Despite the age of the class, penicillins remain the most widely used antibiotics, owing to their broad activity base and good safety profile. They remain the drugs of choice for many clinical uses, including bacterial meningitis, skin infections, pharyngitis, middle ear infections, bronchitis, gonorrhoea, and syphilis, among other infections. They can be taken orally, although different products are absorbed to different degrees and thus, in some cases, injection may be more efficacious. They are well tolerated and toxic side effects are rare, although allergic reactions such as rashes and fever occur in about 10% of patients. Given the age of the group, many penicillins are off-patent, including the class leader of recent years, GlaxoSmithKline's Augmentin (amoxycillin + clavulanic acid), which lost its patent protection in late 2002. There are no products of any significance in development.

Figure 206: Leading penicillins

Brand name	Generic name	Producer	2004 sales
Augmentin	amoxycillin + clavulanic acid	GlaxoSmithKline	$1.3bn
Amoxil	amoxycillin	GlaxoSmithKline	$0.1bn

Source: Company data

Cephalosporins: These are also known as beta-lactams and interfere with synthesis of the bacterial cell wall. Some may be given orally but most are given by injection. They are typically the second choice antibiotic, their main uses being in pneumonia, septicaemia, meningitis, sinusitis and urinary tract infections. Unwanted side-effects are similar to those seen with the penicillins, although they may also cause diarrhoea. The leading class product is Roche's injectable Rocephin, which will see its US patent expire in mid-2005. Note that despite their second-line usage, cephalosporins have a broader spectrum of activity and are more potent than the penicillins.

Figure 207: Leading cephalosporins

Brand name	Generic name	Producer	2004 sales
Rocephin	ceftriaxone	Roche	$1.1bn
Zinnat/Ceftin	cefuroxime axetil	GlaxoSmithKline	$0.4bn
Cefzil	cefprozil	Bristol-Myers Squibb	$0.3bn

Source: Company data

Quinolones: The quinolones, particularly the fluoroquinolones, are the newest class of antibiotic. They work by inhibiting a bacterial enzyme called DNA Gyrase, which prevents bacterial DNA from coiling, so preventing replication. Bayer's ciprofloxacin and J&J/Daiichi's levofloxacin are the most commonly used. The quinolones are broad spectrum but are particularly effective against many gram-negative bacteria, including many organisms that are resistant to penicillin. Taken orally or by injection, their main uses are in urinary tract infections. Unwanted effects are infrequent and usually mild but include gastrointestinal disturbances and skin rashes (photosensitivity). In addition, because of their unique mechanism of action, the bacterial resistance mechanisms that have limited the efficacy of the other main classes have not been replicated. Although resistant strains have developed, the quinolones have experienced strong volume growth as a class. However, value growth has been tempered by generic competition, most notably with the arrival of ciprofloxacin generics in 2003.

Several new products are in development, including Taisho/Schering-Plough's garenoxacin. However, problems associated with the class have been an increasing feature. Generally, the quinolones are not recommended for use in children owing to potential abnormalities in cartilage formation. Pfizer withdrew its new product Trovan following liver toxicity, while GlaxoSmithKline withdrew its product Raxar after reports of cardiac abnormalities. Bayer's Avelox also has warnings regarding QT prolongation (heart arrhythmias) on its US label, so damaging its competitive profile and hindering growth.

Figure 208: Leading quinolones

Brand name	Generic name	Producer	2004 sales
Ciprobay	ciprofloxacin	Bayer	$0.9bn
Levaquin	levofloxacin	Johnson & Johnson	$1.3bn
Cravit	levofloxacin	Daiichi	$0.4bn
Tequin	gatifloxacin	Bristol-Myers Squibb	$0.2bn
Avelox	moxifloxacin	Bayer	$0.5bn
Tavanic	levofloxacin	Sanofi-Aventis	$0.3bn

Source: Company data

Figure 209: Comparative profiles of quinolone antibiotics

Brand name	Cipro	Levaquin	Tequin	Avelox
Generic name	ciprofloxacin	levofloxacin	gatifloxacin	moxifloxacin
Marketer	Bayer	J&J/Sanofi-Aventis	BMS	Bayer
Launch	1986	1997	1999	1999
Clinical profile				
Gram +ve	+	++	+++	+++
Gram –ve	++++	++	++	+++
Respiratory tract	+	++	++	++
Urinary tract	+++	+	+	+
Indications				
Urinary tract	✓	✓	✓	
Chronic bronchitis		✓	✓	✓
Sinusitis	✓	✓	✓	✓
Pneumonia	✓	✓	✓	✓
Skin infections	✓	✓	✓	✓
Gastrointestinal	✓			
Bone and joint	✓			

Source: Company data

Macrolides: Macrolides such as erythromycin have been in use for over 40 years. They interfere with bacterial protein synthesis by attaching to bacterial ribosomes (the cellular constituents that read RNA as a template for protein synthesis). Their spectrum of activity is similar to that of the penicillins (although they are mainly effective against gram-positive bacteria) and they have proven useful alternatives in penicillin-sensitive patients. They are typically administered orally, with the main unwanted side-effects being gastrointestinal disturbances.

Figure 210: Leading macrolides

Brand name	Generic name	Producer	2004 sales
Zithromax	azithromycin	Pfizer	$1.9bn
Biaxin/Klaricid	clarithromycin	Abbott	$1.2bn
n/a	erythromycin	Various	n/a
Ketek	telithromycin	Sanofi-Aventis	$0.3bn

Source: Company data

Resistance conferring opportunity

Poor compliance and over-prescribing, among other reasons, have meant that bacterial resistance to antibiotics is becoming an increasing problem. After years of exposure and consequent mutation, many infections are now becoming resistant to a greater number of drugs. Initially more prevalent in hospital settings, resistance is now an increasing threat in community-acquired infection.

There are several mechanisms of resistance. For example, bacteria have become capable of synthesising beta lactamases that cleave the beta lactams before they can be fully effective. Alternatively, bacterial mutation has meant that initial drug targets have been modified. These resistance mechanisms have primarily limited the use of penicillin, cephalosporins and other beta lactams in the treatment of certain diseases. Resistance to the quinolones is also a growing problem. Target alteration has also limited the use of erythromycin and some other macrolides. Thus, where staphylococcus aureus was in the past effectively treated with methycillin, strains have emerged that are now resistant to this and many other antibiotics (for example, methycillin resistant staphylococcus aureus or MRSA). Equally, enterococcus, a frequently encountered hospital pathogen, now shows resistance to vancomycin that previously had been the antibiotic of last resort.

This presents a major threat to the treatment of disease. Tried and trusted antibiotics may no longer work on bacteria against which they had previously proven efficacious. However, this situation also confers opportunity to new classes of antibiotics that operate through alternative mechanisms. For example, Pfizer's Zyvox, launched in 2000, is designed to treat bacteria resistant to methycillin and vancomycin. Similarly, Sanofi-Aventis' Ketek is the first to market in a new sub-class of macrolides called ketolides, and has been shown to be highly effective against multi-drug resistant strains of streptococcus pneumoniae (MDRSP).

Figure 211: Some instances of bacterial resistance

Bacteria	Disease examples	Resistance	Minimal resistance
Gram positive			
Streptococcus pneumoniae	Pneumonia,	Beta-lactams, macrolides	Quinolones, clavulanic acid
Staphylococcus aureus	Sepsis, pneumonia	Penicillin, vancomycin	Recent quinolones
Enterococci	Urinary tract	Vancomycin	Zyvox
Gram negative			
H. influenzae	Meningitis, earache	Beta-lactams	Quinolones
E. coli	Urinary tract	Quinolones, penicillin	Macrolides

Source: Deutsche Bank

Pipeline products

As described above, many of the compounds in development represent variations within the existing antibiotic classes and are targeted at resistant strains of bacteria. While there is an unequivocal medical need for such alternative treatments, it is important to note that this may nonetheless limit their commercial potential by positioning them as treatments of last resort.

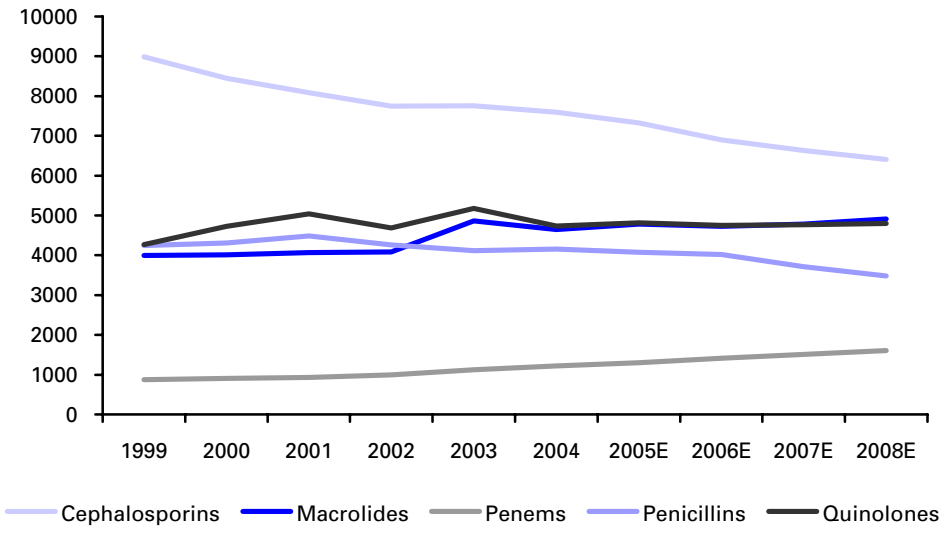
Wyeth's Tygacil is an intravenous antibiotic for the treatment of serious infections caused by both gram-positive resistant bacteria (including resistant staphylococcus aureus) and gram-negative resistant bacteria. In particular, the latter category has proven particularly difficult to treat with newer antibiotics such as Pfizer's Zyvox and Merck's Invanz proving ineffective. Toyoma's garenoxacin also aims to treat both gram-positive and -negative pathogens including penicillin-resistant streptococcus pneumoniae. The product was originally licensed to Schering-Plough in June 2004. However, following Schering-Plough's agreement to market Bayer's US primary care portfolio (including Bayer's marketed quinolone Avelox), US rights for garenoxacin are expected to be sub-licensed to a third party.

Figure 212: Selected pipeline antibiotics

Name	Sponsor	Class/Mechanism	Status	Est filing
Tygacil	Wyeth	glycylcyline	Launch 2005	Approved
dalbavancin	Pfizer*	glycopeptide	Launch 2006	Filed
retapamulin ('833)	GlaxoSmithKline	pleuromutilin (topical)	Phase III	2005
garenoxacin	Schering-Plough/Taisho**	quinolone	Phase III	2006
ceftobiprole (BAL5788)	Basilea/J&J	cephalosporin	Phase III	2006
doripenem	J&J	carbapenem	Phase III	2006
iclaprim	Arpida	folic acid inhibitor	Phase III	2007
DU-6859a	Daiichi	quinolone	Phase II	2007

*Source: Company information *Assumes completion of Vicuron acquisition **US rights to be sub-licensed*

Figure 213: Sales forecasts for key antibiotic classes ($ m)



Source: Wood Mackenzie

Figure 214: Sales forecasts for key antibiotic classes ($ m)

	1999	2000	2001	2002	2003	2004	2005E	2006E	2007E	2008E
Cephalosporins	8986	8445	8089	7748	7754	7596	7322	6896	6635	6407
Macrolides	3998	4009	4064	4082	4862	4646	4781	4726	4779	4908
Penems	876	905	934	1000	1123	1226	1305	1411	1508	1606
Penicillins	4244	4308	4488	4263	4114	4156	4079	4016	3711	3483
Quinolones	4268	4728	5037	4685	5173	4735	4815	4747	4766	4798

Source: Wood Mackenzie

NOTES

Human immunodeficiency virus (HIV)

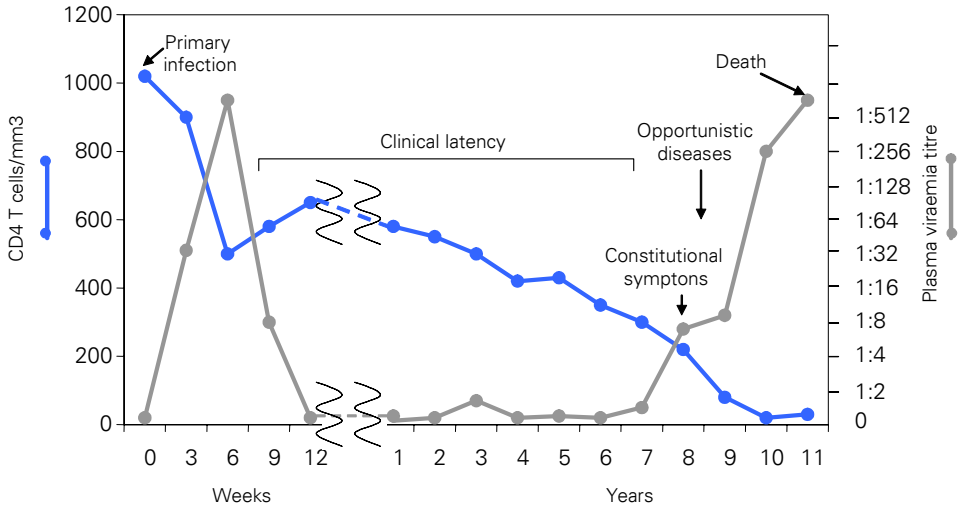
- World market in 2004 worth over $7bn
- Approximately 40 million people infected worldwide including 1.5 - 2 million in the US and Europe
- Growth of approximately 6% per annum; combination therapy key
- GlaxoSmithKline and Bristol-Myers Squibb dominate

Acquired immunodeficiency syndrome (AIDS) is caused by the human immunodeficiency virus (HIV). Affecting over 40 million people worldwide, including an estimated 1.5 – 2 million in the US and Europe, the virus acts by replicating in the white cells of the immune system and destroying them in the process. Shorn of their resistance to disease, HIV-infected individuals become highly susceptible to opportunistic and other infections and it is these secondary infections that are the usual cause of death. Growth of the market for HIV drugs in recent years has been strong, driven by a number of factors. These include the development of new drugs, acceptance that drug treatment has a beneficial effect on prognosis, and the issuance of treatment guidelines promoting the initiation of earlier therapy. The efficacy of current regimens has also aided drug growth and patients are living longer on a high drug regimen. Despite this, it is estimated that of the one million or so infected in the US, only 20–25% currently receive treatment, with over 50% of patients as yet unaware of their condition. Moreover, within the 400,000 or so patient segment currently receiving antiretroviral therapy, new patient starts and discontinuations tend to offset each other such that growth of the treated population is relatively flat.

Physiology

Viruses are small infective agents (virions) essentially consisting of nucleic acid enclosed in a protein coat called a capsid. They are intracellular parasites with no metabolic machinery of their own. Simplistically, viruses operate by attaching themselves to host cell receptors, which then mediate cell entrance generally through endocytosis. The nucleic acid of the virus (which in HIV is a strand of RNA) then uses the host cell's replication machinery to synthesise additional quantities of its own genetic code (nucleic acid), as well as the proteins it needs for assembly of new viral capsids. Host cell death follows, leading to the release of multiple virions, which go on to infect other cells.

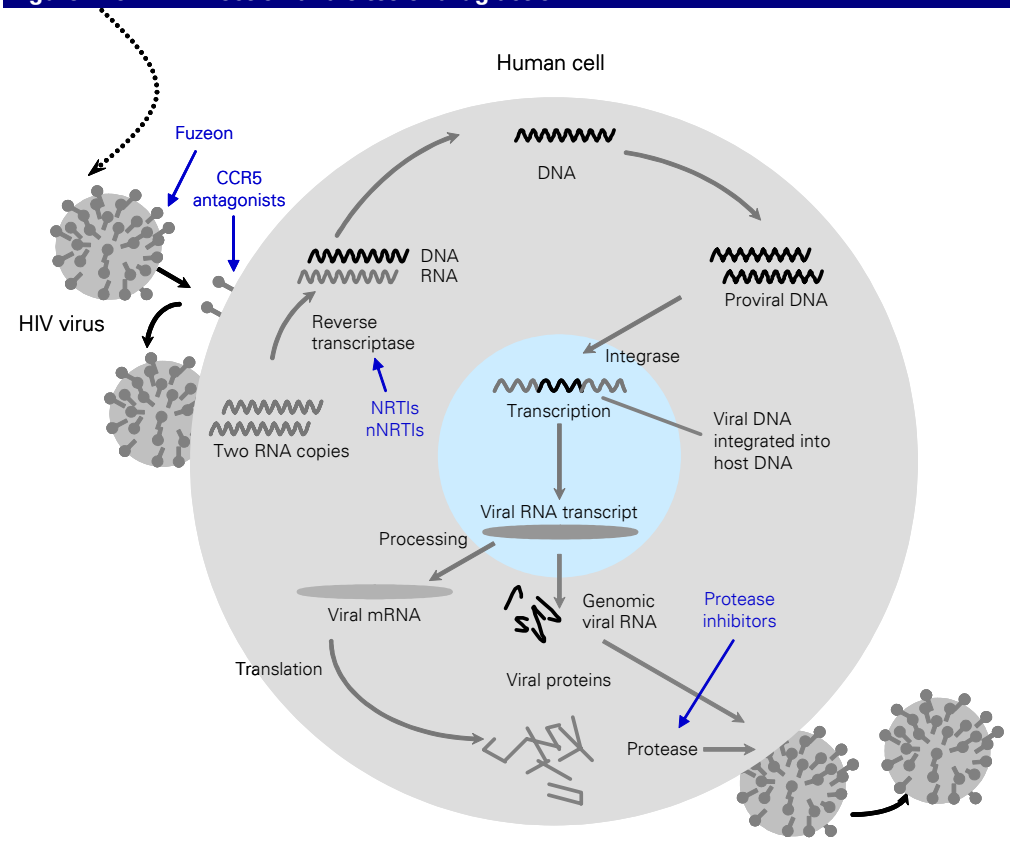
Figure 215: Progression of HIV to AIDS takes a long time



Source: Rang, Dale & Ritter

In a patient infected with HIV, the virus binds to a particular class of white blood cells called helper T-cells or CD4 cells. These normally play a key role in the body's natural immune defences. Once infected, there is a progressive loss of CD4 cells, this being the defining characteristic of HIV infection, and the viral count in the host's blood (the viral load) increases markedly. As antibodies to the infected CD4 cells are produced by the body's still-functioning immune system, the infected CD4 cells are killed and with them the virions. Consequently, the viral load declines sharply. However, because viral replication is error prone, constant mutations occur and, while the human defence system consistently produces antibodies to the new variants, wave after wave of mutations are postulated to gradually deplete the body's ability to respond. Over considerable time, the virus eventually gains the upper hand. The viral load starts to rise and when the body's immune system is no longer able to ward off other opportunistic infections, full-blown AIDS develops. In the absence of drug therapy, death usually follows within two years, caused by a host of opportunistic diseases.

Figure 216: HIV infection and sites of drug action



Source: Rang, Dale & Ritter

Pharmacological treatment

As with antibiotics used against bacteria, the development of drugs to treat HIV has centred around inhibiting metabolic processes that are specific to the virus. To date, treatments have focused on three main mechanisms of action, leading to the emergence of three classes of drug, the nucleoside reverse transcriptase inhibitors, or nRTIs; the non-nucleoside reverse transcriptase inhibitors, or nNRTIs; and the protease inhibitors, or PIs. The mechanism of each is briefly described below and also illustrated by the above diagram. However, it should be stressed that while the discovery of several new drugs to treat the HIV virus has extended the lives and prospects for HIV positive patients, up to 40% of patients are on their third or fourth combination regimen because of therapy failure or resistance.

- **NRTIs**: This class of drug binds to the active site of the reverse transcriptase enzyme. Reverse transcriptase is responsible for transcribing the viral RNA injected into the CD4 cell to DNA. It does so by copying the viral RNA block by block or nucleotide by nucleotide. However, when an nRTI is used, it binds to the enzyme and is inserted into the DNA chain instead of a nucleotide. Its dysfunctional properties prevent further growth of the DNA chain, thereby stopping the creation of a new virus. The value of the class in 2004 was around $3.9bn. Side effects of several of these drugs include neuropathy (nerve death), intestinal intolerance, pancreatitis, insomnia and anaemia. Importantly, GSK's Epivir shows minimal toxicity, which together with a twice-daily dosing regimen and unique resistance profile, have made it the drug of choice.

Figure 217: Leading nRTIs

Brand name	Generic	Manufacturer	2004 sales
Retrovir (AZT)	zidovudine	GlaxoSmithKline	$0.1bn
Epivir (3TC)	lamivudine	GlaxoSmithKline	$0.5bn
Zerit	stavudine	Bristol-Myers Squibb	$0.3bn
Ziagen	abacavir	GlaxoSmithKline	$0.3bn
Videx	didanosine	Bristol-Myers Squibb	$0.3bn
Emtriva	emtricitabine	Gilead	$0.1bn
Viread	tenofovir	Gilead	$0.8bn
Combivir	zidovudine + lamivudine	GlaxoSmithKline	$1.0bn
Trizivir	zidovudine + lamivudine + abacavir	GlaxoSmithKline	$0.6bn
Epzicom	lamivudine + abacavir	GlaxoSmithKline	launch
Truvada	emtricitabine + tenofovir	Gilead	launch

Source: Company data

- **NNRTIs**: This class of drug actually binds to the reverse transcriptase enzyme, but not at its active site. Rather, it binds at another site and in doing so prevents the enzyme from functioning. Given a more favourable side-effect profile, the role of nNRTIs in therapy in 2004 was around $1.0bn. Side effects include headaches and rashes. Sustiva's once-a-day dosing has positioned it as the drug of choice.

Figure 218: Leading nNRTIs

Brand name	Generic	Manufacturer	2004 sales
Sustiva	efiravenz	Bristol-Myers Squibb	$0.6bn
Viramune	nevirapine	Boehringer Ingelheim	$0.4bn

Source: Company data

- **Protease inhibitors:** This class of drug acts on a different enzyme to the other two classes. The human host cell replicates many new viral proteins after the proviral DNA has been inserted into the human DNA. These proteins are used to assemble new virus before release into the body. In order to assemble the virus, these protein chains need splicing into smaller units. This is the job of the protease enzyme, which is inhibited from functioning by this class of drug. The value of the class in 2002 was around $2.3bn. There are many side effects, not least gastrointestinal disturbances, nausea and lipodystrophy (fatty humps develop on patients' backs).

Figure 219: Leading protease inhibitors

Brand name	Generic	Manufacturer	2004 sales
Invirase	saquinavir	Roche	$0.1bn
Crixivan	indinavir	Merck	$0.3bn
Viracept	nelfinavir	Roche/Pfizer	$0.4bn
Norvir	ritonavir	Abbott	$0.2bn
Kaletra	lopinavir + ritonavir	Abbott	$0.9bn
Agenerase	amprenavir	GlaxoSmithKline	<$0.1bn
Lexiva	fosamprenavir	GlaxoSmithKline	<$0.1bn
Reyataz	atazanavir	Bristol-Myers Squibb	$0.4bn

Source: Company data

- **Fusion inhibitors:** The newest class of HIV drug to market, the fusion inhibitors attempt to prevent the HIV virus from infecting the CD4 cell by interfering with a protein on the surface of the viral envelope and thereby preventing the virion's attachment to the target cell. The only currently marketed product in this class is Roche/Trimeris' Fuzeon which generated sales of roughly $140m in 2004. Additional fusion inhibitors are also in development, but these interfere with a different target, namely the CCR5 receptor on the cell surface. However, the aim of the CCR5 inhibitors is similar – to prevent entry of the virus into the cell.

Treatment protocol

Antiretroviral therapy has changed dramatically in recent years. Data suggesting that treatment with three drug regimens could – in theory – completely suppress viral replication have driven the acceptance of combination therapy as the standard method of treatment for HIV-infected patients. Initially, treatment guidelines recommended the use of two nRTIs with one protease inhibitor. However, concerns over metabolic side effects associated with PIs have seen some switching to the use of an nNRTI instead. Currently the US guidelines recommend the following combinations as preferred initial regimens:

- **nNRTI-based:** Sustiva + (Epivir or Emtriva) + (Retrovir or Viread)
- **PI-based:** Kaletra + (Epivir or Emtriva) + Retrovir

Given the number of drugs taken, compliance with such highly active anti-retroviral therapy (HAART) is also a major issue. Consequently, the drug manufacturers have sought to develop combination tablets, such as GSK's Combivir and Trizivir and Gilead's Truvada.

Because of the degree of mutation of the HIV virus, viral resistance remains a major issue and problem. Despite the development of several classes of drug, a successful outcome from treatment cannot be assured. As such and in an effort to limit resistance to current drugs, there has been considerable debate as to when it is most appropriate to start treatment. Current US guidelines are as follows:

Figure 220: US HIV treatment protocol

Clinical category	CD4 and HIV count	Recommendation
Symptomatic (AIDS evident)	Any value	Treat
Asymptomatic	CD4<200 cells/mm^3	Treat
Asymptomatic	CD4 between 201-350 cells/mm^3	Treatment should be offered if not initiated
Asymptomatic	CD4>350 cells/mm^3 and HIV RNA >100,000 copies per ml	Treatment recommendation unclear
Asymptomatic	CD4>350 cells/mm^3 and HIV RNA <100,000 copies per ml	Defer treatment

Source: National Institutes of Health

Clinical end-points

Given that the key measurements for any HIV drug will be its impact on viral load and with it, recovery in the number of T-helper cells, the two primary clinical measures are the CD4 and viral load counts. In addition, the count should be taken after several different periods of treatment in order to establish whether the impact on HIV is sustained or transitory.

Pipeline products

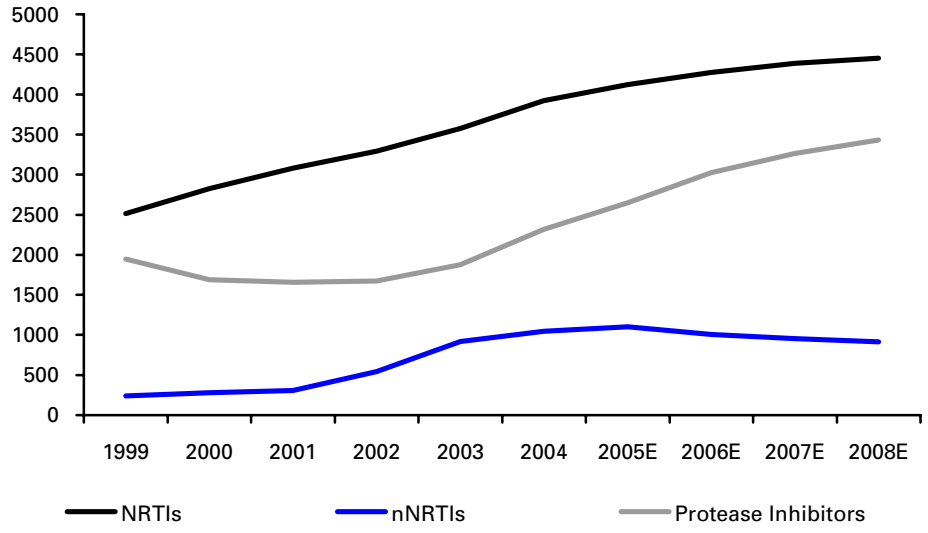
A number of HIV drugs are in development with the most interesting of these being the CCR5 inhibitors. The CCR5 receptor is found on the surface of CD4 cells and is required by most strains of HIV to facilitate entry of the virus into the cell. By competitively binding to the CCR5 receptor, the CCR5 antagonists prevent infection of the CD4 cell. Three CCR5 inhibitors are in development with the most advanced of these being maraviroc from Pfizer and aplaviroc from GSK. Additionally, several new NRTIs and PIs are in development which aim to provide efficacy against resistant strains of virus.

Figure 221: Key HIV pipeline products

Name	Sponsor	Class/Mechanism	Status	Est filing
Aptivus (tipranavir)	Boehringer Ingelheim	Protease inhibitor	Launch 2005	Approved
maraviroc (UK-427,857)	Pfizer	CCR5 antagonist	Phase III	2007
aplaviroc ('140)	GlaxoSmithKline	CCR5 antagonist	Phase III	2007
vicriviroc (SCH-D)	Schering-Plough	CCR5 antagonist	Phase II	2007
640385	GlaxoSmithKline	Protease inhibitor	Phase II	>2007
BMS-488043	Bristol-Myers Squibb	CD4 attachment inhibitor	Phase II	>2007
PRO542	Progenics	CD4 attachment inhibitor	Phase II	>2007

Source: Deutsche Bank

Figure 222: Sales growth of HIV classes ($ m)



Source: Wood Mackenzie

Figure 223: Sales growth of HIV classes ($m)

	1999	2000	2001	2002	2003	2004	2005E	2006E	2007E	2008E
NRTIs	2514	2824	3082	3291	3576	3923	4123	4274	4389	4453
nNRTIs	240	281	308	543	917	1047	1103	1006	953	915
Protease Inhibitors	1947	1687	1656	1671	1877	2317	2651	3025	3264	3433

Source: Wood Mackenzie

Viral hepatitis

- World market in 2004 including vaccines valued at roughly $4bn
- Two major markets – hepatitis C (HCV) and hepatitis B (HBV)
- Over 350 million people infected with HBV and 170 million with HCV
- Major players include Schering-Plough, Roche and GlaxoSmithKline

Viral hepatitis is a major cause of disease and death worldwide. At least five different clinically important variants have been discovered, of which the two most significant, hepatitis C (HCV) and hepatitis B (HBV), account for up to 80% of chronic disease. The vast majority of carriers are not aware that they are infected.

Physiology

Hepatitis B and C are typically contracted through the blood and thus are most commonly associated with intravenous drug use or infected blood products. Although both can be transmitted sexually, it is estimated to be 100 times easier to pass on than HIV. As its name suggests, the virus congregates and replicates in liver cells (or hepatocytes), using the host cells' apparatus to replicate. There are several different forms of the virus, including both acute and chronic, which are clinically defined by the duration or severity of the infection. In acute hepatitis, the viral infection may last up to six months, during which time patients develop only a few mild symptoms, such as fatigue, malaise, anorexia, and in about 25% of cases, jaundice. Most acute sufferers experience minimal liver cell damage.

For HBV, about 65% of patients recover completely. However, approximately 10% of adults and up to 90% of infants do not clear the virus within six months and develop chronic or persistent infection. Without treatment, these patients are likely to carry the disease for the rest of their lives. While many of these may show no symptoms for long periods of time, if at all, a significant proportion will go on to develop liver cirrhosis or cancer of the liver, dying prematurely. At the present time, it is thought that up to 350 million people worldwide have chronic HBV. Although the vast majority are in South East Asia and Africa, where as much as 8-10% of the population is infected, there are estimated to be 1.25 million chronic sufferers in the United States and over three million in western Europe. In the US, roughly 10% of chronic liver disease and cirrhosis are secondary effects of chronic HBV infection.

By contrast, in HCV, a far higher percentage of people infected fail to clear the virus within six months. Up to 80% develop chronic infection, of whom a significant minority will suffer from liver cirrhosis and liver cancer. The number of patients who develop chronic HCV means that it is now the leading cause of liver transplants in the US. It is estimated that there are now over 170 million carriers worldwide, predominantly in Africa, South East Asia and Latin America, with some 12 million people in the major western economies confronting the disease. Importantly, of the 2.7 million infected in the US, only 20% have been diagnosed and only 5% have elected to receive treatment.

Pharmaceutical treatment of chronic viral HBV

No known drug can consistently eradicate HBV. Current therapeutic options include antiviral agents and immunomodulatory agents, such as interferon, that affect viral replication and alter the immune response. A huge potential market does, however, make development of an effective prophylactic commercially desirable.

- **Interferons**: Traditionally, treatment has been based around the use of the alpha-interferons, which were introduced by Roche and Schering-Plough in the US market in 1992. These drugs act by stimulating the immune system and in 33% of patients, lead to a complete loss of HBV DNA and normalisation of certain liver enzymes (serum aminotransferases). A small percentage of responders relapse following the cessation of therapy (this is in marked contrast with HCV, where almost 50% relapse). Interferon is, however, very expensive. Side effects also result in the discontinuance of therapy in up to 10% of patients.
- **Antivirals**: Aside from interferon, certain nucleoside reverse transcription inhibitors (NRTIs), which are traditionally used for HIV treatment, have been found to have a therapeutic effect. Most significant among these is GlaxoSmithKline's lamivudine, or Zeffix brand. Three-year clinical data have shown that 65% of patients taking this drug experience a loss of viral antigen, although resistance (not yet seen to be clinically relevant) is a feature. The drug is taken orally once daily (an advantage over injectable interferon) and costs substantially less. Zeffix realised sales in 2004 of $240m. In addition, Bristol-Myers recently won approval for a new nucleoside analogue, Baraclude (entecavir), which demonstrated superiority over lamivudine in treatment-naïve patients, with 81% of patients achieving a viral load <300 copies/ml. Baraclude is also approved for use in lamivudine-resistant patients.

Beyond treatment of the disease, there is also a substantial market for hepatitis vaccines, which in 2004 was worth approximately $1bn. Two vaccines are currently available, both of which are based on recombinant forms of the HBV surface antigen. These are GlaxoSmithKline's Engerix B and Merck's Recombivax. Dosage is in the form of three injections over six months and results in protection for over 90% of healthy persons.

Pharmaceutical treatment of chronic viral HCV

As with HBV treatment, that of HCV relies heavily on the use of interferons. However, in contrast with HBV, where the product is used to boost the immune response, in HCV, interferon acts to inhibit viral replication. As with HBV, the objective of treatment is to achieve an undetectable viral load and normal liver enzyme levels six months after the cessation of therapy, that is, attain a sustained response. It is also important to recognise that in HCV, there are six different viral genotypes. Crucial here is that the two most prevalent genotypes, 1a and 1b, which account for 70% of chronic HCV infections, are also the hardest to treat. This is seen from analysis of response profiles, where patients with genotype 2 or 3 achieve a 40% response with interferon alone, against a 10% response rate for genotype 1.

Until recently, the traditional standard of treatment for HCV was alpha interferon and an adjunct called Rebetrol (ribavirin). In the US, Schering-Plough alone had rights to this combination, bundling the two products together in a package called Rebetron. In effect, this froze its main competitor, Roche, out of the US market.

However, the virus often responded poorly to this conventional therapy, most likely as a result of the fast rate at which injectable interferon is broken down by the body and, consequently, its low bioavailability. In an attempt to overcome this, both Schering-Plough and Roche have developed new forms of interferon. Called pegylated interferon, Schering-Plough's PEG-Intron and Roche's Pegasys have a molecule of polyethylene glycol attached to

them, which reduces the rate at which they degrade in the body. In addition, they can be given once a week compared to traditional regimens, which require injections three times a week.

Schering-Plough received approval for PEG-Intron in January 2001, followed by approval for the drug in combination with ribavirin approximately one year later. Roche received approval for Pegasys in October 2002, followed by approval for its own ribavirin (called Copegus) to be used in combination with Pegasys two months thereafter. Since its launch, Pegasys rapidly gained market share to become the class leader. While there is little hard clinical evidence differentiating the two drugs, Pegasys success is thought to be related to its perceived better tolerability as well as the broader clinical dataset supporting its efficacy. However, Schering-Plough recently initiated a head-to-head PEG-Intron versus Pegasys study, albeit this is unlikely to report for several years.

Figure 224: Comparison of Pegasys and PEG-Intron efficacy

	Pegasys		PEG-Intron		Pegasys + Ribavirin		PEG-Intron + Ribavirin	
Genotype	**Make-up**	**Sustained response**	**Make-up**	**Sustained response**	**Make-up**	**Sustained response**	**Make-up**	**Sustained response**
Genotype 1	63	28	70	14	n.a.	46	68	42
Non-1	37	58	30	51	n.a.	76	32	82
Total	100	39	100	25	100	56	100	54

Source: European Association for the Liver; American Association for Study of Liver Diseases

Clinical end-points

The two key markers for hepatitis B and C are viral load, which is measured by examining serum levels of HCV/HBV RNA and the level of particular liver enzyme, most significantly, hepatic transaminase ALT. The objective of treatment is that a sustained response is attained, that is, that there is no sign of viral RNA in the serum six months after treatment is discontinued, and that liver enzyme levels have returned to normal. Trial data is typically taken at 24 and 48 weeks. And remember, in HCV, the genotype population is crucial to the response.

NOTES

Influenza

- World market, including vaccines, worth $1.1bn in 2004
- 25-40 million cases in the US per annum
- Leading product is Tamiflu (Roche)

Influenza or 'flu' is an infection of the lungs caused by the highly contagious influenza virus. This virus spreads from person to person by tiny droplets produced by coughing and sneezing. Other symptoms experienced include a combination of fever, sore throat and aches. The virus is most active between November and March when the human immune system in the Northern Hemisphere is at its weakest. The effect is exacerbated by large gatherings that take place around Christmas, which provide easy routes for the virus to reach new targets and spread quickly. It is estimated that between 25 and 40 million people are infected in the US during the flu season each year.

Physiology

The influenza virus is an RNA virus and comprises an RNA core surrounded by a lipid envelope with two glycoproteins (proteins with sugar molecules attached), called neuraminidase and hemaglutinin, protruding from it. On inhalation of the virus, its hemaglutinin binds to sialic acid on the surface of the epithelial cells that line the respiratory tract. This binding prompts the cell to internalise the virus. The cell's protein synthesising machinery is then used by the virus to produce multiple copies of its core and the two key glycoproteins. These are packaged into the lipid envelope made from the membrane of the infected epithelial cell. The hemaglutinin on the surface of the new virus again binds to the host cell membrane via a sialic acid bond. Finally, the neuraminidase protein cleaves to the host cell wall and the infection spreads.

The body's immune system produces antibodies to the two viral glycoproteins when it has been infected and protects the individual from future infections by the same virus. However, these proteins mutate easily, either as a result of 'antigenic drift' or 'antigenic shift'. Consequently, they can be slightly different from those previously encountered by the body. This prevents the bodies' existing antibodies from neutralising them and results in a new infection.

Pharmacological treatment

Until 1999, there was no effective treatment for all strains of influenza. In severe cases, flu can deteriorate to pneumonia, a more life threatening disease and around 1% of sufferers are hospitalised. However, most patients recover within one to two weeks, a time frame that can be significantly reduced by the novel flu drugs, *Relenza* and *Tamiflu,* if they are taken within 48 hours of infection.

Figure 225: Treatments in the market

	Tamiflu	Relenza
Generic name	oseltamivir	zanamavir
Producer	Roche	GlaxoSmithKline
Sales 2004	$275m	<$50m
Dosing	Oral tablet	Inhaler device
US approvals	Treatment and Prophylaxis	Treatment
Symptom benefit	1.3 to 1.4 day symptom reduction	1 to 2.5 day symptom reduction
Side effects	Nausea in 5% over placebo	As per placebo
Resistance	No resistance develops	1% develop resistance
Administration	Within 48 hours	Within 48 hours

Source: Deutsche Bank Securities Inc. estimates and company information

These compounds are neuraminidase inhibitors. They block the active site of the neuraminidase protein by mimicking the host cells' sialic acid, thereby preventing attachment to the host cell wall and thereby preventing the viruses from spreading to surrounding cells and exacerbating the infection. They can also be used as an effective prophylactic (a protective).

Flu vaccines have also been around for many years and are generally given approximately six weeks before flu season in an effort to reduce (although not eliminate) the likelihood of becoming ill. Given the frequent mutations of the flu virus, these vaccines are reformulated each year to combine different strains of virus. Following the withdrawal of Wyeth's FluShield, Sanofi-Aventis (Fluzone) and Chiron (Fluvirin) have become the dominant players in this field.

In mid 2004, Chiron's license for its UK flu vaccine manufacturing plant was suspended due to manufacturing deficiencies, but the company plans to resume supplying the market for the 2005/6 flu season. In addition, the Chiron suspension prompted GlaxoSmithKline (which previously only sold its vaccine, Fluraix, outside the US) to seek FDA approval for its product.

Clinical end-points

The primary end-point in the treatment group is the reduction in length of symptoms, that is, how quickly do patients recover from the disease? As a prophylactic, the objective of treatment is disease prevention relative to placebo.

Central nervous system disorders

While recent years have seen scientists make good progress in their understanding of the human brain and central nervous system (CNS), diseases of the CNS and, indeed, the mechanisms of the brain remain poorly understood. Pathways are complex and because of the intricacy of messenger pathways and complicated feedback mechanisms, few CNS disorders are well defined. Yet, CNS disorders represent a major source of disease and physician visits and as a result, a major source of pharmaceutical industry revenues. Indeed, in 2004, drugs for CNS disorders generated revenues totalling an estimated $50bn.

Over the following pages, we review the leading disorders, most significantly depression and schizophrenia. However, prepare to be frustrated. Cause and effect are poorly understood, receptor sub-types are numerous and as a consequence, the beginner is almost certain to be somewhat bemused. Consequently and in order to provide some type of overview, we have started this section with an overview of the principal roles played by the leading neurotransmitters found in the central nervous system.

Leading neurotransmitters of the CNS

- **L-glutamate** is the principal and ubiquitous excitatory transmitter in the CNS. It is widely and fairly uniformly distributed and its concentration in the CNS is much higher than in the periphery. It is derived from glucose and glutamine and is stored in synaptic vesicles (nerve-ending storage dumps). Its release is typically controlled by the concentration of calcium, while its actions are mainly terminated by carrier mediated re-uptake into the nerve terminals. Glutamate acts upon four different categories of receptor, the most significant of which are the NMDA and AMPA receptors. It is believed to play an important role in learning/memory, epilepsy and excitotoxicity or brain ischaemia (stroke), given that, somewhat surprisingly, it is highly neuro-toxic.
- **GABA** (gamma amino butyric acid) is the main inhibitory transmitter in the brain. It is formed from glutamate by the action of glutamic acid decarboxylase and broken down by GABA-transaminase. As with glutamate, its actions are generally terminated following its neuronal reuptake. Virtually all neurons are sensitive to its inhibitory effect. It acts on two types of receptors, GABA A and B. As an inhibitory transmitter, it plays a vital role in dampening CNS activity. Drugs such as benzodiazapine sedatives and barbiturates act by enhancing its receptor binding, thereby causing sedation and tranquillity. GABA agonists are also used as anti-convulsants and anti-epileptics.
- **Noradrenaline** (norepinephrine) has both inhibitory and excitatory effects. As with most CNS transmitters, its exact role is unclear. Among other effects, it is believed to increase wakefulness and alertness and it has been suggested that a functional deficiency of noradrenaline leads to depression, while an excess results in mania. Outside mood, noradrenaline plays a key role in the regulation of blood pressure.

- **Dopamine** is a neurotransmitter, as well as being a precursor of noradrenaline. Among other functions, it plays an important role in motor function and mood. Monoamine oxidase (MAO) and COMT (catechol-O-methyl transferase) break it down. Dopamine acts on two main receptor classes, excitingly entitled D1 and D2 type. Given its importance to motor control, it plays a key role in Parkinson's disease, in which patients suffer from a deficiency of dopamine. There is also increasing evidence that excess dopamine has a role in schizophrenia. Dopamine is also associated with vomiting (emesis). Thus, nearly all dopamine receptor agonists (stimulators) cause vomiting and nausea as a side effect, while dopamine antagonists (depressors) act as anti-emetics.
- **Serotonin** (5-hydroxytryptamine or 5HT) is produced in neurons from dietary tryptophan. Following its release, it is largely recovered by neuronal uptake, which may be inhibited by specific serotonin reuptake inhibitors (SSRIs), an important class of antidepressant. As with dopamine, serotonin is degraded by MAO. There are several classes of 5HT receptor located in different concentrations and regions of the brain. The three most significant are 5HT1, 5HT2 and 5HT3. 5HT1 is predominantly inhibitory in its effect. Thus, antagonism can be used to treat depression. By contrast, 5HT3 plays a role in nausea (emesis). Overall, 5HT is associated with wakefulness, mood, hallucinations, sleep and behaviour.
- **Acetylcholine** plays an important role in the CNS. It has a largely excitatory role, acting on two classes of receptors described as muscarinic and nicotinic. The main functions ascribed to cholinergic pathways are related to arousal and learning. As such, certain neurodegenerative disorders, such as Parkinson's and Alzheimer's, are associated with abnormalities in cholinergic pathways. Muscarinic receptors act to block acetylcholine release and to mediate the main behavioural effects associated with acetylcholine (learning and memory). Their antagonism or blockage has been seen to lead to amnesia. Nicotinic receptors are seen to potentiate the release of other excitatory transmitters, such as dopamine and glutamate.

Figure 226: Summary of the leading CNS neurotransmitters and their properties

Neurotransmitter	Receptors	Functional role	Disease involvement	Drug types	Key enzymes
Glutamate	NMDA, AMPA	Excitatory	Stroke, epilepsy	None significant	GABA aminotransferase
GABA	GABA Types A & B	Dampens CNS activity	Epilepsy, sedation	Benzodiazepines, barbiturates	GAD (creation), GABA transaminase
Serotonin (5-HT)	5HT 1-4	Hallucinations, mood, alertness	Depression, anxiety	SSRIs, TCAs, MAOIs	MAO (degrades)
Noradrenaline	Beta-adreno receptors	Alertness,	Depression, anxiety	SSRIs, TCAs	Created by DOPA decarboxylase
Dopamine	D1 and D2	Motor control, mood	Parkinson's, schizophrenia	Dopamine agonists, antagonists,	MAO and COMT degrade
Acetylcholine	Muscarinic and nicotinic	Learning, memory	Alzheimer's	Cholinesterase inhibitors	Acetylcholinesterase (degrades)

Source: Deutsche Bank

Schizophrenia

- World market worth approximately $11bn in 2004
- Growth in excess of 10% per annum
- Around 1% of the population globally affected
- Leading products include Zyprexa (Eli Lilly), Risperdal (Johnson & Johnson) and Seroquel (AstraZeneca)

Schizophrenia is a disorder of the mind that is believed to arise from a neurochemical imbalance in the brain. Derived from the Greek and meaning 'split mind', it is a relatively common condition affecting approximately 1% of the population at some point in their lives. Some 15-30 new cases are diagnosed per 100,000 people annually. It develops mainly in young people, affecting men and women equally, although the symptoms seem to appear earlier in males (generally between the ages of 15-24). Sadly, it often drives the patient to attempt to commit suicide. The recent development of atypical drugs used in its treatment with fewer side effects has driven strong growth of the market in recent years and is expected to continue to do so.

Schizophrenia is characterised by an array of symptoms that are divided crudely into positive and negative. Negative symptoms can co-exist with positive from the start, or may develop later, perhaps as a consequence of treatment.

Figure 227: Schizophrenia – positive and negative symptoms

Positive symptoms	Negative symptoms
Hallucinations (voices)	Withdrawal from society
Delusions (often paranoid)	Flattening of emotions
Thought disturbances (irrational)	Apathy
Incoherence	Low self-esteem

Source: Deutsche Bank

While the cause of schizophrenia remains unclear, it is believed to involve a combination of genetic and environmental factors. As such, it is seen as a neurodevelopmental disorder rather than a neurodegenerative one (for example, Alzheimer's and Parkinson's). In first degree relatives, the incidence of schizophrenia is 10%, strongly supporting a hereditary and thus genetic disposition to the disease. Some theories suggest that it arises as a consequence of a viral infection of the foetus while in the uterus.

Physiology

As with almost all other CNS disorders, an accurate physiology of schizophrenia is not known. However, pharmacological evidence suggests that it is associated with dopamine overactivity, as dopamine agonists have been seen to induce schizophrenia and antagonists control it. There are two main families of dopamine receptors in the brain, classed as D1 and D2, but the dopamine receptors relevant to the actions of the anti-psychotic drugs mainly belong to the D2 family (namely D2, D3 and D4). Receptor function is, however, also dependent on where in the brain the receptors are located. Consequently, side effects with drug treatment are common. Thus, the "typical" anti-psychotics act by inhibiting the action of dopamine on D2 receptors in the mesolimbic area of the brain, with a favourable impact on the positive symptoms of schizophrenia (but little on the negative). Their impact on D1 and D2 receptors elsewhere has, however, meant that most of the 'typical' anti-psychotics developed to date have distinct side effects. These fall into three main categories:

- **Extrapyramidal side effects (EPS).** These are the most problematic and unwanted effects of treatment and consist of involuntary movements (muscle spasms, twitching, shaking), which often resemble the symptoms of Parkinson's disease.
- **The release of prolactin.** Because dopamine plays a role in inhibiting the secretion of this hormone, dopamine antagonists tend to see a rise in plasma prolactin concentration levels. The result is breast swelling, pain and lactation in both men and women.
- **Autonomic side effects**. Effects on receptors in the periphery can cause blurred vision, increased pressure in the eye and urinary retention, as well as other disorders.

Beyond dopamine, the observation that LSD can induce hallucinations by acting on 5HT receptors has led to the development of 'atypical' anti-psychotic therapy. Serotonin (or 5HT) is known to have some modulatory effects on dopaminergic pathways and, by inhibiting 5HT, the side effects associated with the earlier or 'typical' pharmacological treatments have been reduced. Indeed, it has also been suggested that by blocking 5HT, the negative symptoms associated with schizophrenia are reduced.

Pharmacological treatment

As pharmacological treatment has developed, it has led to the emergence of two distinct classes of drugs, the 'typical' and 'atypical' anti-psychotics. The distinction between the two is not well defined, but rests on the incidence of EPS side effects, efficacy against hard-to-treat patients and efficacy against negative symptoms. The typical anti-psychotics represent the earlier drugs discovered and used in therapy. They generally act by inhibiting the action of dopamine in the brain and work well against positive symptoms. However, their effect on the negative symptoms associated with schizophrenia is often more muted and side effects, particularly EPS, tend to be significant. Early drugs in this class included the phenothiazines (for example, chlorpromazine). These were subsequently displaced following the 1958 discovery of haloperidol, which showed a much-reduced incidence of extrapyramidal side effects. It is of note that haloperidol remains the comparator of choice when assessing the benefits of new drugs in development.

Figure 228: Classes of schizophrenia treatment

Typical	Atypical
chlorpromazine	clozapine (Clozaril)
sulpiride (Dogmatil)	risperidone (Risperdal)
haloperidol (Haldol)	olanzapine (Zyprexa)
	quetiapine (Seroquel)
	ziprasidone (Geodon)
	apriprazole (Abilify)

Source: Deutsche Bank

More recently, the development of the atypical anti-psychotics has helped to drive the dramatic growth of the overall class and it is these drugs that dominate today's markets. While side effects remain a key negative, their incidence has been much reduced, while containment of both positive and negative features of schizophrenia has been improved.

Figure 229: Leading atypical anti-psychotics

Brand name	Generic name	Manufacturer	2004 sales
Zyprexa	olanzapine	Eli Lilly	$4.4bn
Risperdal	risperidone	Johnson & Johnson	$3.1bn
Seroquel	quetiapine	AstraZeneca	$2.0bn
Geodon	ziprasidone	Pfizer	$0.5bn
Abilify	aripiprazole	Bristol-Myers Squibb	$0.6bn

Source: Company data

- **Clozaril**: The first atypical anti-psychotic, Clozaril, is now off-patent. The drug is associated with certain blood disorders (agranulocytosis) and, as such, patients need regular blood checks. However, Clozaril is the only drug approved in treatment-resistant cases.
- **Zyprexa**: Launched in 1996, Zyprexa is the leading anti-psychotic by value on the market. Sales have benefited from the strength of Eli Lilly's position in CNS, which has been built on the back of its now off-patent anti-depressant, Prozac. Zyprexa is an isomer of clozapine, with activity on dopaminergic, 5HT and muscarinic receptors. It has good activity against both positive and negative symptoms of schizophrenia, needs to be taken once a day and has fewer EPS side effects than haloperidol. However, it does cause weight gain in some patients and may increase the risk of developing diabetes. This issue in particular has contributed to the drug's sliding market share in the US market.
- **Risperdal**: Despite its 1994 US launch, a higher incidence of EPS (particularly at higher dosages) and the need for dose titration (gradual increases in dosage to find the appropriate level) have caused Risperdal to lose ground to newer entrants in this category. Taken once a day, the drug acts on both dopaminergic and 5HT receptors, so treating both the positive and negative effects of schizophrenia.
- **Seroquel**: Although Seroquel got off to a slow start following its US launch in 1997, it has steadily gained market share since and is now challenging Risperdal for market leadership. In particular, the drug has been successful due to its placebo-like incidence of EPS. It is also effective against both positive and negative symptoms and does not appear to induce weight gain.
- **Geodon**: Launched in 2001 after long delays at the FDA, Geodon is a novel serotonin and dopamine antagonist that does not induce weight gain. However, its uptake has been slow due to concerns about its effect on the heart (QT prolongation) that emerged during clinical trials and unproven efficacy relative to other class products.
- **Abilify**: The most recent entrant to the market, Abilify was launched in late 2002 and benefits from once-daily dosing, minimal EPS side effects (albeit these may rise at higher doses) and no effect on weight gain. On the negative side, Abilify may cause nausea. It is a partial dopamine and serotonin agonist, thus treating the positive and negative effects of schizophrenia.

Figure 230: Comparison of leading antipsychotics (and pipeline products)

	Seroquel	Zyprexa	Risperdal	Abilify	Geodon	bifeprunox	asenapine
Generic	quetiapine	olanzapine	risperdone	aripiprazole	ziprasidone	bifeprunox	asenapine
Company	AstraZeneca	Lilly	J&J	Bristol-Myers	Pfizer	Solvay/Wyeth	Akzo/Pfizer
US launch	1997	1996	1994	2002	2001	Phase III (filing 2006)	Phase III (filing 2007)
Dosing	Twice daily	Once daily	Twice daily	Once daily	Twice daily	Once daily	Twice daily
Placebo-like EPS	Yes	No	No	Yes (except at higher doses)	No	Yes (?)	Yes (?)
Placebo-like prolactin (linked to sexual dysfunction)	Yes	No	No	Yes	No	Yes (?)	No (?)
Weight-neutral	Yes	No	No	Yes	Yes	Yes (?)	Yes (?)
Other	Bolded warning on cataracts	Adverse lipid effects		Increased incidence of nausea	Bolded warning on QtC prolongation)	Triglyceride reduction	

Source: Deutsche Bank, Company information

Clinical end-points

Key to clinical trials is the impact of any new molecule on the positive and negative symptoms of schizophrenia, together with a favourable side-effect profile. These will be assessed subjectively by clinicians and patients and marked according to the Positive and Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS). Control trials measuring the performance of the new entity against haloperidol (and perhaps olanzapine and risperidone) ought also to be undertaken and show a favourable outcome.

Pipeline products

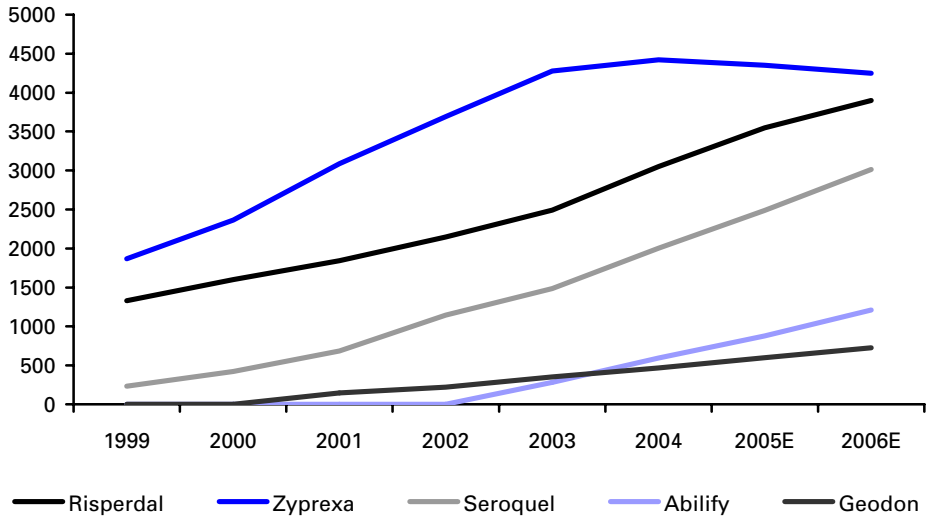
There are several new atypical anti-psychotics in development. Amongst these are J&J's paliperidone ER which is a risperidone metabolite due to be filed in 2005; bifeprunox, a serotonin and dopamine partial agonist developed by Solvay and licensed to Wyeth (US) and Lundbeck (Europe); and asenapine, a serotonin and dopamine antagonist developed by Akzo Nobel and licensed to Pfizer. Based on the data available, we expect that bifeprunox will demonstrate efficacy in line with the class with no/minimal sexual dysfunction and EPS and a weight-neutral profile. For asenapine, the limited data released thus far suggest the drug may have class-like efficacy against positive symptoms but potentially a leading profile against negative symptoms. However, we expect it may be associated with sexual dysfunction and a class-like diabetes risk.

Figure 231: Key late stage schizophrenia drugs

Name	Sponsor	Class/Mechanism	Status	Est filing
paliperidone ER	Johnson & Johnson	5HT2 & D2 antagonist	Phase III	2005
bifeprunox	Solvay/Wyeth/Lundbeck	5HT1A agonist & D2 partial agonist	Phase III	2006
asenapine	Akzo/Pfizer	5HT2 & D2 antagonist	Phase III	2007
talnetant	GlaxoSmithKline	NK3 receptor antagonist	Phase II	>2007
osanetant	Sanofi-Aventis	NK3 receptor antagonist	Phase II	>2007
Lonasen	Dainippon	5HT2 & D2 antagonist	Phase II	>2007
SM13496	Sumitomo/Merck	5HT2A & D2 antagonist	Phase II	>2007

Source: Deutsche Bank & Company information

Figure 232: Growth of Leading Schizophrenia Drugs ($ m)



Source: Company data, Deutsche Bank estimates

Figure 233: Growth of Leading Schizophrenia Drugs ($ m)

		1999	2000	2001	2002	2003	2004	2005E	2006E
Risperdal	Johnson & Johnson	1328	1603	1845	2146	2493	3050	3545	3899
Zyprexa	Eli Lilly	1868	2366	3087	3689	4277	4420	4350	4250
Seroquel	AstraZeneca	232	424	685	1145	1487	2004	2490	3013
Abilify	Bristol-Myers Squibb	0	0	0	0	283	594	880	1210
Geodon	Pfizer	0	0	149	222	353	467	600	725

Source: Deutsche Bank

NOTES

Parkinson's disease

- World market in 2004 worth around $2bn
- Limited effective long-term treatment
- Leading products include Mirapex (Pfizer) and Requip (GSK)

Parkinson's disease is the second-most common adult-onset neuro-degenerative disease. It affects about 4 million people worldwide, or roughly 1–2% of people over the age of 65. It is a progressive disorder of movement that occurs mainly in the elderly, the classic signs of which are tremor, rigidity and the suppression of voluntary movements. The disease shows no hereditary tendency, but is often preceded by stroke or viral infection and appears to be more prevalent in men than in women. Memory impairment and cognitive dysfunction are rarely encountered in the early stages of Parkinson's disease, although 30% of sufferers eventually develop some form of dementia. Depression is also a common feature.

Physiology

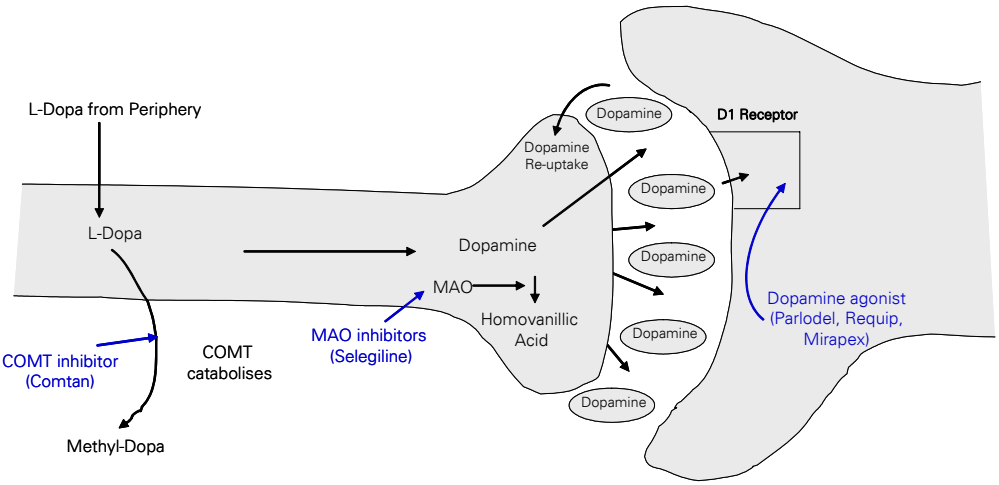
The main feature of Parkinson's disease is the progressive destruction of dopamine-producing cells in a particular part of the brain associated with motor control, called the substantia nigra. Dopamine plays a key role in motor control (movement), both directly and by controlling (depressing) the level of acetylcholine released in other parts of the brain. Post-mortem studies have revealed that the dopamine content of this part of the brain is extremely low, at less than 10% of normal levels. It is estimated that the characteristic Parkinson's disease symptoms develop once 70% of the dopaminergic neurons in the substantia nigra have been destroyed. Hence, the balance of dopamine and acetylcholine in the brain is distorted, with the result that messages to the muscles become garbled. While the exact cause of this physiological change is unknown, a consensus is now emerging that the disease is caused by oxidative stress and metal toxicity.

Pharmacological treatment

Given that the apparent cause of Parkinson's disease is a lack of dopamine in the brain, current pharmacological treatment is aimed at increasing the level of dopamine, either directly or through slowing its metabolism in the brain.

First-line treatment relies heavily on L-dopa, a dopamine precursor that can cross the blood-brain barrier. Because conversion of L-dopa outside the brain normally sees about 95% of it metabolised before it arrives in the brain, L-dopa is nearly always combined with a decarboxylase inhibitor. However, because this decarboxylase inhibitor cannot pass into the brain, L-dopa is rapidly broken down once in the CNS. Unfortunately, while L-dopa can be seen to provide immediate benefit to patients at the early stage of the disease, as time progresses, its effectiveness declines. The drug also has significant, albeit slowly developing side effects, not least involuntary writhing movements, which tend to develop within two years of treatment, and sudden rigidity (which is believed to arise as the brain's ability to store the dopamine it is given deteriorates). Sadly, after five years of treatment, over 60% of patients will be little better than they were at the inception of treatment.

Figure 234: Action of dopamine and drugs to treat Parkinson's



Source: Deutsche Bank

Beyond direct treatment with L-dopa, current pharmacological treatment also includes various dopamine agonists and drugs that inhibit the enzymes that degrade dopamine. These are typically used in combination with L-dopa and include inhibitors of both monoamine oxidase (MAO) and catechol-O-methyl transferase (COMT). However, no treatment has as yet shown itself capable of fully or permanently restoring motor function. Importantly, dopamine agonists can be given as monotherapy before initiating L-dopa with the hope of extending the effectiveness of L-dopa therapy. Equally, COMT inhibitors also extend the effectiveness of L-dopa and may reduce side effects.

As a class, there are few drugs that have attained significant sales. This largely reflects the maturity of current drugs and the absence of any dramatic advances in medication. Many of the currently available drugs are off-patent.

Figure 235: Key drugs used to treat Parkinson's disease

Brand	Generic	Action	Producer	2004 Sales
Parlodel	bromocriptine	Dopamine agonist	Novartis	$0.1bn
Requip	ropinirole	Dopamine agonist	GlaxoSmithKline	$0.2bn
Mirapex	pramipexole	Dopamine agonist	Pfizer/Boehringer Ingelheim	$0.4bn
Permax	pergolide	Dopamine agonist	Lilly	$0.2bn
Comtan	entacapone	COMT inhibitor	Novartis	$0.1bn
Sinemet	L-dopa/carbidopa	Dopamine precursor	Bristol-Myers Squibb	$0.1bn
Madopar	L-dopa/benserazide	Dopamine precursor	Roche	$0.2bn

Source: Company data

Pipeline products

One of the more interesting products in development for Parkinson's is a dopamine agonist which is delivered via a steady release patch. The patch, called Neupro and developed by Schwarz Pharma, is used once a day and ensures steady plasma dopamine level. It was filed with the FDA in early 2005. Elsewhere, Lundbeck and Teva recently received regulatory approval for Azilect, a MAO B inhibitor.

Alzheimer's disease

- World market in 2004 worth nearly $2.5n
- Growth currently over 20%
- Affects 10% of the over-65 population, with 15 million people afflicted worldwide
- Leading products include Aricept (Pfizer/Eisai) and Exelon (Novartis)

Alzheimer's disease (AD), first characterised by Alois Alzheimer in 1907, is a gradual progressive dementia affecting both cognition and behaviour. It is characterised by a loss of short-tem memory and deterioration in behaviour and intellectual performance. The exact physiology is unknown and no cure exists. Although drugs may reduce symptoms and progression for a time, the disease is usually fatal. Alzheimer's is generally thought of as a disease of old age, because most cases present themselves after the age of 65. The disease affects 10% of people over the age of 65 and almost 50% of those of 85 years and over. In 2002, AD was listed as the eighth-leading cause of death in the US, killing 59,000 people; however, the real figure is thought to be higher, given that AD is often not reported on death certificates. Perhaps more significantly, the estimated costs of dealing with the disease are put at a staggering $100bn per annum. We would also note that several genes encoding important enzymes and proteins associated with Alzheimer's disease have now been discovered, implying a genetic predisposition to the disease.

Physiology

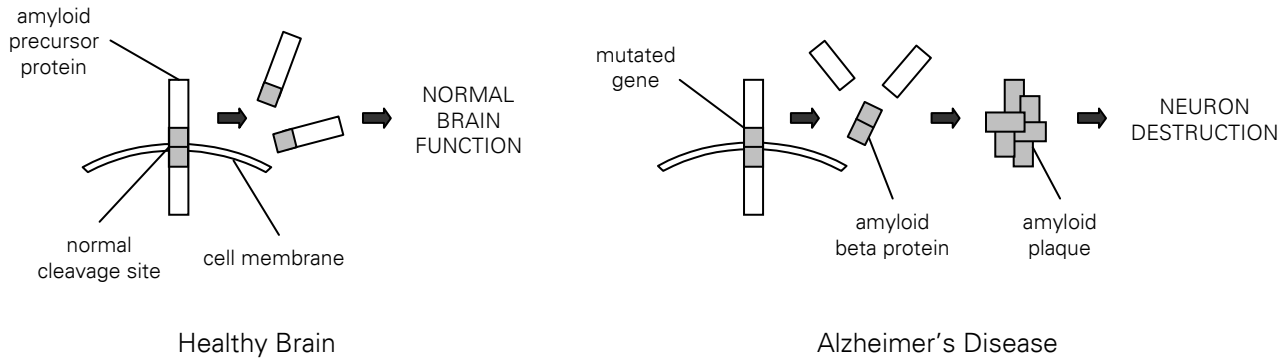
Alzheimer's disease is associated with shrinkage of brain tissue and localised loss of neurons (nerve fibres) in certain parts of the brain. Two microscopic features are characteristic of the disease, namely, the existence of extracellular 'amyloid' proteins, which are similar in nature to starch and which form plaques around brain neurons; and intra-neuronal meshes of filaments (Tau proteins), called neurofibrillary tangles. Altered processing of amyloid protein from its precursor is now recognised as key to the pathogenesis of the disease.

In the brains of normal individuals, a long chain glycoprotein called amyloid precursor protein (APP) is cleaved to produce a smaller protein which aids brain function. However, mutation of the APP gene gives rise to amyloid proteins (called amyloid beta proteins) of different chain lengths. One of these, in particular, leads to the creation of plaques, which ultimately result in the destruction of brain neurons, either directly or as a result of an immune response to the developed plaque.

As neurons are injured or die, neurotransmitter concentrations diminish. In particular, the concentration of acetylcholine and the number of cholinergic neurons are reduced. Consequently, drug therapy to date is largely directed at increasing the concentration of acetylcholine in the brain by preventing its metabolism by the enzyme acetylcholinesterase and so preserving neuronal communication and function. Although such an approach cannot cure the disease, it has been seen to slow the rate of deterioration in Alzheimer's patients by six to twelve months.

Importantly, several genes associated with Alzheimer's disease have now been identified and it is hoped that as knowledge of the illness develops, therapies aimed at prevention will be developed.

Figure 236: Plaque formation in Alzheimer's disease



Source: Dipiro, Talbert, Uee, Matzke, Wells and Posey

Pharmacological treatment

As stated, the focus of current drugs available for treatment of Alzheimer's has been to improve the concentration of acetylcholine in the brain. Acetylcholine is believed to have a role in learning and short-term memory and its concentration in particular areas of the brain is known to be reduced in Alzheimer's patients. To date, three drugs have been approved for use in Alzheimer's, each of which works by inhibiting acetylcholinesterase and, consequently, the breakdown of acetylcholine. Products of this nature are likely to dominate the market for several years. However, there are several other drugs in development that look at different mechanisms of action. These include drugs that inhibit the enzymes that cleave APP at the wrong point and drugs directed at mitigating the immune response that arises as a result of plaque formation resulting in neuronal destruction.

Figure 237: Current acetylcholinesterase Inhibitors

Brand name	Aricept	Exelon	Reminyl
Generic	donepezil	rivastigmine tartrate	galantamine
Manufacturer	Pfizer/Eisai	Novartis	J&J/Shire
Sales 2004	$1.4bn	$0.4bn	$0.3bn
Side effects	Nausea, vomiting, diarrhoea	Nausea, vomiting, diarrhoea, weight loss	Nausea, vomiting, diarrhoea
Cognition	Delays symptoms of AD by 6 -12 months	Most effective in moderate to severe	Dual mechanism of action also nicotinic
Dosing	Once a day	Twice a day	Twice a day

Source: Company data

Aside from the acetylcholinesterase inhibitors, Forest recently won US approval for Namenda (memantine) which was developed by the German company, Merz, and has been sold in Europe under the name Ebixa since 20002. Namenda is an NMDA receptor antagonist and is designed to offer neuroprotective effects in patients with AD. Because of its unique mechanism of action, it may also be given in combination with the acetylcholinesterase inhibitors. The drug is currently approved for the treatment of moderate-to-severe AD, but a supplementary application for the mild-to-moderate population is currently under regulatory review.

Clinical end-points

As with many CNS disorders, end-points for trials designed to assess the impact of new molecules on Alzheimer's disease rest heavily on the assessment of clinicians. Various structured interview-based scales measuring efficacy against placebo exist. Most significant among these are the Alzheimer's Disease Assessment Scale (ADAS) and the Clinicians Interview Based Impression of Change (CIBIC).

Pipeline products

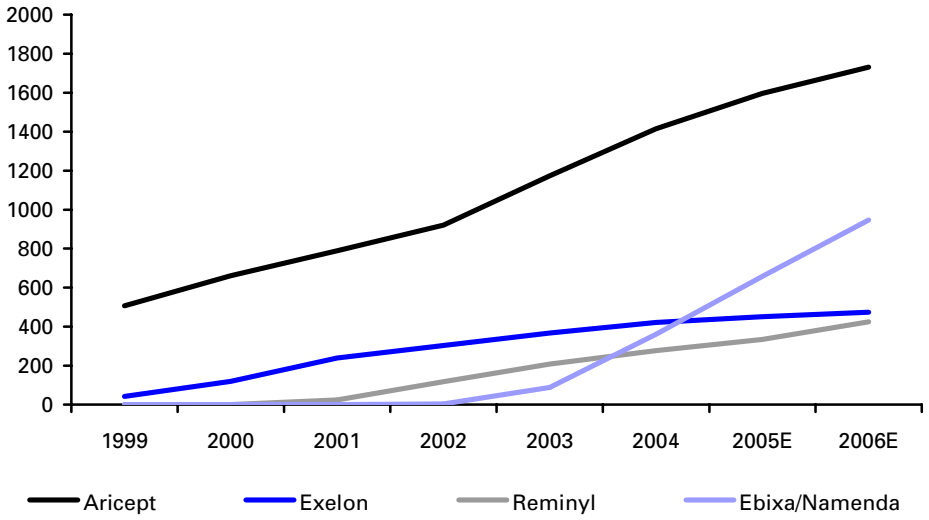
Several products are in development for Alzheimer's disease, including novel compounds that act as beta amyloid inhibitors. Most are still in early stage studies with regulatory filings unlikely before 2007 at best. It is important to emphasise, however, that drug development in this area (like much neurological research) has historically been risky, with many drugs failing to meet safety or efficacy requirements in clinical trials. One of the most recent examples is Elan/Wyeth's highly touted drug, AN-1792, which had its Phase I trial suspended following instances of inflammation in the central nervous system.

Figure 238: Key pipeline products for Alzheimer's

Name	Sponsor	Mechanism	Status
xaliproden	Sanofi-Aventis	Non-peptide neurotrophic agent	Phase III
Alzhemed	Neurochem	Glycosaminoglycan mimetic	Phase III
Flurizan	Myriad Genetics	NFkB modulator	Phase II/III
SRA333	Wyeth	5HT-1A receptor antagonist	Phase II

Source: Deutsche Bank & Company information

Figure 239: Sales growth of leading Alzheimer drugs ($ m)



Source: Company data, Deutsche Bank estimates

Figure 240: Sales growth of leading Alzheimer drugs ($ m)

		1999	2000	2001	2002	2003	2004	2005E	2006E
Aricept	Eisai/Pfizer	508	661	788	921	1174	1415	1596	1731
Exelon	Novartis	43	120	239	304	367	422	452	474
Reminyl	Shire/J&J	0	0	25	119	208	277	335	425
Ebixa/Namenda	Forest/Lundbeck	0	0	0	4	55	384	623	918

Source: Deutsche Bank

NOTES

Affective Disorders (Depression)

- World market in 2004 worth roughly $14bn
- Value growth slowed due to patent expiration of class-leading products.
- Leading products include Zoloft (Pfizer) and Effexor (Wyeth)

Affective disorders are characterised by changes in mood (depression or mania). Depression is the most common state, ranging from mild to severe, or psychotic depression, which may be accompanied by hallucinations and delusions. Symptoms of depression include emotional and biological components, emotional including things such as misery, apathy, low motivation and low self-esteem, while the biological response includes a loss of appetite and sleep disturbance, among other symptoms. There are two types of depressive syndrome, namely, *unipolar* (75% of cases), in which mood swings are always in the same direction, and *bipolar,* in which depression alternates with mania (manic depression). There is a strong genetic tendency in bipolar disorders.

The true prevalence of depressive disorders is unknown, although various bodies have reported that around 17% of the population have a history of a major depressive disorder at some point in their lifetime and more than 10% an episode within the past year. Depression is two to three times as frequent in females as it is in males and is most evident in adults between the ages of 25 and 44. The most frequent complication of depression is suicide and it is estimated that about 15% of those with unrecognised or poorly treated depression commit suicide.

Physiology

As with most illnesses of the CNS, the physiological cause of affective disorders is unclear. The main theory of depression is, however, that it arises as a consequence of a functional deficit of monoamine transmitters at certain sites in the brain. In contrast, mania is due to functional excess. In part, this theory is supported by the positive impact that drugs with a known ability to facilitate monoaminergic transmission have on depression, although many studies have shown this theory to be over-simplistic.

The key neurotransmitters with a role in depression and mania appear to be the monoamines, that is, serotonin (5-HT) and noradrenaline. Consequently, the pharmacological approach to alleviation of the symptoms has been to develop drugs that impact upon the level of these monoamines in particular regions of the brain. Several different classes of drugs have been developed over the years, including the tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin re-uptake inhibitors (SSRIs), and serotonin and norepinephrine re-uptake inhibitors (SNRIs). It is the latter two classes which account for the lion's share of today's world market by value.

- **Tricyclic antidepressants.** These act by inhibiting the uptake of noradrenaline and/or serotonin (5-HT) by monoaminergic nerve terminals, thus facilitating transmission. They act by competing with the binding site of the amine carrier protein. However, most TCAs also have an impact on other types of receptor, leading to troublesome side effects. These include dry mouth, blurred vision, constipation, sedation and urinary retention. They also have significant adverse interactions with other drugs. Taken in overdose, they can be fatal, something of a disadvantage given their use by a class of patients that frequently has suicidal tendencies.

- **Monoamine oxidase inhibitors (MAOIs).** Monoamine oxidase has two main functions - to control the concentration of noradrenaline and 5-HT within the nerve terminal and to inactivate ingested amines. MAOIs bind irreversibly to one or both forms of the cerebral enzyme, monoamine oxidase (MAO-A or B), so increasing stores of noradrenaline, dopamine and 5-HT in nerve terminals. Inhibition of MAO type A correlates most strongly with antidepressant activity, because it is this enzyme that has the strongest affinity for 5-HT. MAOIs were among the first anti-depressant drugs to be developed. However, significant side effects arose, in part because of the effect of these drugs on the action of MAO outside the CNS. Consequently, they have largely been displaced by the TCAs and SSRIs. As with TCAs, overdose can be fatal.
- **Selective serotonin re-uptake inhibitors (SSRIs).** These show greater selectivity for 5-HT than either the TCAs or MAOIs. While their efficacy in treating the symptoms of depression is no greater than that of the TCAs, a much improved side-effect profile has seen them become the leading class of anti-depressants. As with other classes of drugs, it is typically two to four weeks before a therapeutic benefit is seen. Common side effects include nausea, insomnia, weight loss and loss of libido; yet their toxicity is less than that of other classes. Importantly, the efficacy and side-effect profile of the SSRIs has seen them used in a variety of other, largely anxiety-related, disorders, such as panic attacks, anxiety disorders and obsessive-compulsive disorder. Increased usage of these drugs for anxiolytic indications has helped drive the overall size of the market for anti-depressants.
- **Serotonin and norepinephrine re-uptake inhibitors (SNRIs).** Like the SSRIs, the SNRIs offer similar efficacy in relieving depression symptoms while providing a more tolerable side effect profile compared to the TCAs. In particular, the SNRIs are often associated with a lower risk of sexual side effects and weight gain. Until recently, there was only one marketed SNRI, namely Wyeth's Effexor XR. However, in late 2004 Eli Lilly won approval for its new SNRI Cymbalta, which is expected to increase competition in this market.

Figure 241: Leading anti-depressants

Brand name	Generic name	Manufacturer	Class	Sales 2004
Prozac	fluoxetine	Eli Lilly	SSRI	$0.6bn
Paxil/Seroxat	paroxetine	GlaxoSmithKline	SSRI	$1.9bn
Zoloft	sertraline	Pfizer	SSRI	$3.4bn
Effexor	venlafaxine	Wyeth	SNRI	$3.3bn
Wellbutrin	bupropion	GlaxoSmithKline	NDRI	$1.4bn
Celexa	citalopram	Forest Laboratories	SSRI	$1.0bn
Lexapro	escitalopram	Forest Laboratories	SSRI	$2.0bn
Cymbalta	duloxetine	Lilly	SNRI	launch

Source: Company data

- **Other atypicals.** Beyond these main categories of anti-depressant, there are other drugs such as GSK's Wellbutrin (bupriopion) which target different neurotransmitters. Wellbutrin is a weak inhibitor of norepinephrine and dopamine re-uptake and as a consequence is often used as an add-on therapy to an SSRI. However, it offers a good side effect profile with low risk of sexual side effects and weight gain. Although GSK's twice-daily formulation of Wellbutrin now faces generic competition, the company has introduced a once-daily version, Wellbutrin XL, which has retained over 50% of the bupropion market since launch.

Other indications

Outside affective disorders, anti-depressants have also found increasing use in anxiety-related indications. As stated, this broadening of the indication base has helped drive the growth of the entire class. Additional indications often include the following:

- **Panic disorder**: Panic disorder begins as a series of unexpected panic attacks, involving an intense terrifying fear similar to that caused by life-threatening danger. The attacks are followed by at least a month of persistent concern about having a further attack. Secondary to the panic attack, many patients subsequently develop agoraphobia.
- **Obsessive-compulsive disorder (OCD):** OCD requires the presence of obsessions/compulsions that are severe enough to cause marked distress, to be time consuming and to cause significant impairment in social or occupational functioning. Individuals suffering often recognise that their obsessions (for example, cleanliness) or compulsions are excessive or unreasonable and attempt to ignore or suppress them. Over 50% of those suffering OCD typically also suffer from another major psychiatric disorder.
- **Anxiety:** Historically, anxiety disorders have largely been treated with benzodiazepines (e.g. Valium). These act as GABA (gamma amino butyric acid) agonists, GABA having an inhibitory effect on the activity of certain CNS pathways and, consequently, a calming/sedating influence. However, several of the SSRIs have been seen to have anxiolytic properties, in particular those whose strongest effect is on 5-HT. SSRIs are increasingly emerging as first-line therapy because of better tolerability and lower risk of dependency. They are, however, significantly more expensive than classical benzodiazepine therapy.
- **Social phobias**: The essential feature of social phobia is a marked and persistent fear of social or performance situations in which embarrassment may occur. Unlike other anxiety disorders, the reason for the fear is clearly identifiable, although the patient can do little to control it.

Pipeline products

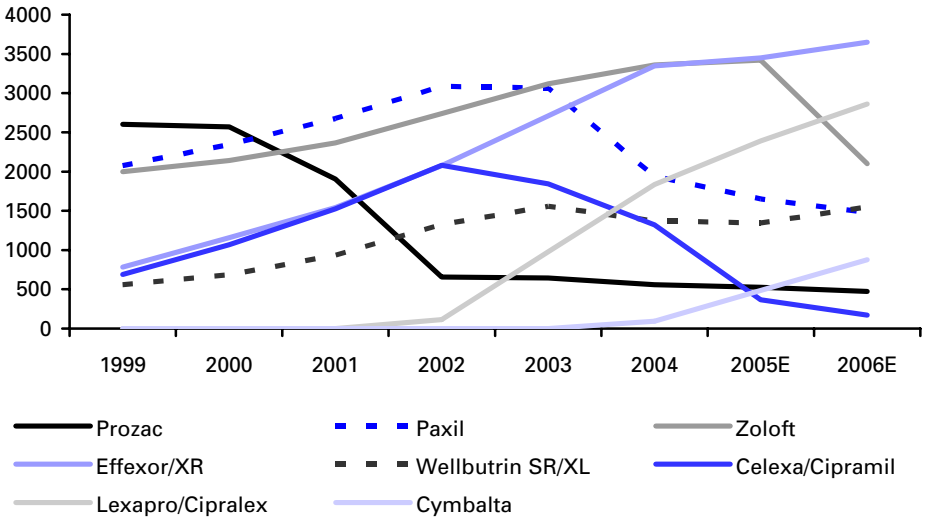
With a half dozen SSRIs on the market, pipeline products in the depression category either represent new entrants to the less developed SNRI or NDRI classes or alternatively drugs which incorporate new mechanisms of action. In this latter group are the NK1 antagonists including GSK's 597599. However, we note this class has struggled to demonstrate significant efficacy, with a number of late-stage compounds such as Merck's aprepitant being dropped in this indication. Additionally, both Merck and GSK are developing triple re-uptake inhibitors which target re-uptake of serotonin, norepinephrine and dopamine. Neither company's product, however, is expected to reach the market significantly ahead of the end of the decade.

Figure 242: Key pipeline products for depression

Name	Sponsor	Class	Status	Est filing
DVS-233	Wyeth	SNRI	Phase III	2006
SR 58611	Sanofi-Aventis	Beta 3 agonist	Phase III	2006
353162	GlaxoSmithKline	NDRI	Phase II	2007
597599	GlaxoSmithKline	NK1 antagonist	Phase II	>2007
372475	GlaxoSmithKline	NDSRI	Phase II	>2008
DOV 216,313	Merck	NDSRI	Phase II	>2008

Source: Deutsche Bank

Figure 243: Sales growth of leading antidepressants ($m)



Source: Company data, Deutsche Bank estimates

Figure 244: Sales growth of leading antidepressants ($m)

		1999	2000	2001	2002	2003	2004	2005E	2006E
Prozac	Eli Lilly	2602	2571	1906	656	645	558	525	475
Paxil	GlaxoSmithKline	2075	2345	2675	3085	3067	1939	1650	1481
Zoloft	Pfizer	1997	2139	2364	2742	3118	3361	3420	2100
Effexor/XR	Wyeth	781	1159	1542	2077	2712	3348	3450	3650
Wellbutrin SR/XL	GlaxoSmithKline	558	684	932	1324	1557	1370	1345	1549
Celexa/Cipramil	Lundbeck/Forest	690	1070	1526	2081	1845	1321	366	170
Lexapro/Cipralex	Lundbeck/Forest	0	0	0	113	977	1834	2390	2862
Cymbalta	Eli Lilly	0	0	0	0	0	94	485	875

Source: Deutsche Bank

Attention deficit hyperactivity disorder (ADHD)

- Worldwide market worth nearly $2bn in 2004
- Approximately 3-5% of school aged children diagnosed with ADHD
- Market dominated by extended-release formulations of older compounds

Attention deficit hyperactivity disorder (ADHD) is the most common behavioural disorder among school-age children. It is estimated to affect 3-5% of children, and is seen as much as ten times more often in boys than in girls. The condition is characterised by three key behaviours – inattentiveness, hyperactivity and impulsiveness – which diminish the patient's ability to function in normal areas of life. In addition, while traditionally considered a childhood disease, recent evidence suggests residual symptoms may persist into adulthood.

ADHD is often difficult to diagnose and treat, due to the lack of observable physiological signs, combined with a broad range of characteristic symptoms. Moreover, many ADHD-type behaviours may be linked to other causes, ranging from mild seizures to emotional disturbances. ADHD may also coexist with neurological conditions such as anxiety disorders or depression.

Given these complexities, the American Psychiatric Association has outlined specific diagnostic criteria in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM IV). An ADHD diagnosis requires that children exhibit signs of inattention and/or hyperactivity and impulsivity that adversely affect their ability to function in at least two environments, such as school, home or social settings. The behaviour must appear before age seven, be excessive in comparison to that expected in children of the same age and must persist for at least six months. The full criteria are outlined in the Figure overleaf.

It is worth noting that, while similar to the DSM-IV guidelines, the diagnostic criteria used in Europe are slightly narrower. Specifically, the European definition, which is based on the *International Classifications of Diseases* (ICD-10), requires that the child exhibit all three symptoms of inattention, hyperactivity and impulsivity. This, in combination with greater European scepticism regarding the treatment of ADHD with stimulant drugs, helps to explain the lower incidence (~1.5% versus ~5%) of the condition in Europe.

Physiology

The cause of ADHD is unknown. The condition appears to run in families, with one in four affected children having a parent previously diagnosed with ADHD. In addition, children whose mothers utilised alcohol, cigarettes or other drugs during pregnancy are at a heightened risk of developing ADHD. However, dietary factors – once thought to cause hyperactivity – have been proven to be uncorrelated.

Recent research has begun to suggest possible neurological abnormalities associated with ADHD. Imaging studies using PET (positron emission tomography) scans have indicated a possible dopamine deficit due to the upregulation of proteins known as dopamine transporters. In addition, there appear to be malfunctions in certain parts of the brain, including areas responsible for concentration and the switching off of automatic responses.

Figure 245: Diagnostic criteria for ADHD

A) Either (1) or (2):
   1) Six (or more) of the following symptoms of inattention have persisted for at least six months to a degree that is maladaptive and inconsistent with developmental level:
      – often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
      – often has difficulty sustaining attention in tasks or play activities
      – often does not seem to listen when spoken to directly
      – often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)
      – often has difficulty organising tasks and activities
      – often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
      – often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools)
      – is often easily distracted by extraneous stimuli
      – is often forgetful in daily activities
   2) Six (or more) of the following symptoms of hyperactivity-impulsivity have persisted for at least six months to a degree that is maladaptive and inconsistent with developmental level:
      Hyperactivity
      – often fidgets with hands or feet or squirms in seat
      – often leaves seat in classroom or in other situations in which remaining seated is expected
      – often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
      – often has difficulty playing or engaging in leisure activities quietly
      – is often "on the go" or often acts as if "driven by a motor"
      – often talks excessively
      Impulsivity
      – often blurts out answers before questions have been completed
      – often has difficulty awaiting turn
      – often interrupts or intrudes on others (e.g., butts into conversations or games)

B) Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years.

C) Some impairment from the symptoms is present in two or more settings (e.g., at school and at home).

D) There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.

E) The symptoms do not occur exclusively during the course of a pervasive developmental disorder, schizophrenia or other psychotic disorder and are not better accounted for by another mental disorder.

Source: Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)

Pharmacological treatment

Current clinical practice usually combines stimulant drugs with behavioural and cognitive therapies. Methylphenidate, first introduced in 1955 as Ritalin, is typically the drug of choice. Amphetamine compounds, such as dextroamphetamine, are used as second-line agents. In addition, Shire has gained success with its product, Adderall XR, which is a long-acting combination of four different amphetamine salts.

Given the long-expired patent protection on these drugs, current branded products are primarily formulation modifications of the traditional stimulants. This is perhaps a more significant strategy in this class of drugs, because its users are primarily children, who must take the mid-day dose while at school. Complicating the dosing regimen is the fact that methylphenidate and amphetamine are class II "scheduled" drugs, meaning that they are government-controlled substances with specific regulations for distribution and dispensing. Thus, companies have achieved significant sales for once-daily premium-priced formulations, despite the presence of cheaper generic alternatives.

In the methylphenidate category, there are three key extended release drugs – Concerta (J&J), Metadate CD (UCB) and Ritalin LA (Novartis). Concerta leads this group by a wide margin, likely as a result of being first to market and enjoying the marketing strength of Johnson & Johnson. Metadate and Ritalin LA which were introduced one and two years later, respectively, offer a different pharmacokinetic profile, as they combine separate immediate-

release and delayed-release components; however, neither has captured a significant share of the market.

Shire's Adderall is the second major competitor in this therapeutic area. The amphetamine-based drug's success is largely due to its favourable pharmacokinetic profile, which enabled Shire to market it as a long-acting agent from its initial launch. However, in anticipation of pending generic competition, Shire developed a so-called extended release formulation, Adderall XR. Interestingly, the actual prescribing instructions of these two versions differ only slightly, with many patients on Adderall taking the drug once daily and other patients on Adderall XR taking the drug twice daily.

Within the traditional stimulant market, there is little evidence of any overwhelming winners with regard to efficacy or ease of use. The market dynamic, however, has changed with the launch of Lilly's Strattera which is the first non-scheduled product in this category. However, after an initial rapid uptake, Stattera's market share appears to have plateaued, largely due to a slower onset of action and more modest efficacy relative to the stimulants. In addition, the FDA recently added a warning to Strattera's label regarding a risk of liver toxicity, which is unlikely to help sales trends in a market that is increasingly sensitive to safety issues.

Figure 246: Leading stimulants for ADHD

Product	Generic	Company	Dosing	2004 sales
Concerta	methylphenidate	J&J	1x/day*	$0.7bn
Metadate CD	methylphenidate	UCB	1x/day*	<$0.1bn
Ritalin	methylphenidate	Novartis	2-3x/day	$0.1bn
Adderall/XR	mixed amphetamine salts	Shire	varies	$0.6bn
Strattera	atomoxetine	Lilly	1-2x/day	$0.7bn

**Despite "once-daily" labelling, often taken 2x/day.*
Source: Company data

Clinical end-points

Clinical trial requirements are not as well established for ADHD as for other indications, as many of the existing drugs never underwent rigorous clinical testing before approval. This is evidenced by the variety of diagnostic rating scales used in recent trials. Among these are the Conner's Inattention/Overactivity with Aggression Scale (IOWA), the Conner's Global Index Scale (TCGIS) and the ADHD Rating Scale-IV (ADHD-RS). In fact, Lilly developed its own parent-rated diary to help measure the efficacy of Strattera.

Pipeline products

With its market-leading Adderall XR franchise soon to face generic competition, Shire remains the most active company in this area. Amongst the products in its portfolio are MethyPatch, a transdermal methylphenidate patch, which should be re-filed with the FDA in 2005 following an earlier 'non-approvable' letter in April 2003; SPD503, a reformulated version of an old anti-hypertensive drug which has demonstrated efficacy in ADHD and, if approved, could offer the second non-scheduled treatment option; and SPD465, an even longer-acting formulation of Adderall. In addition, Shire has licensed rights to an amphetamine derivative NRP104 from New River Pharmaceuticals. Phase III data showed a significant improvement on the ADHD-RS and Conner's scale, while a head-to-head Phase II trial demonstrated comparable efficacy to Shire's Adderall XR. Importantly, NRP104 is designed to be non-addictive, and thus could be positioned as a non-scheduled, yet still potent treatment for ADHD.

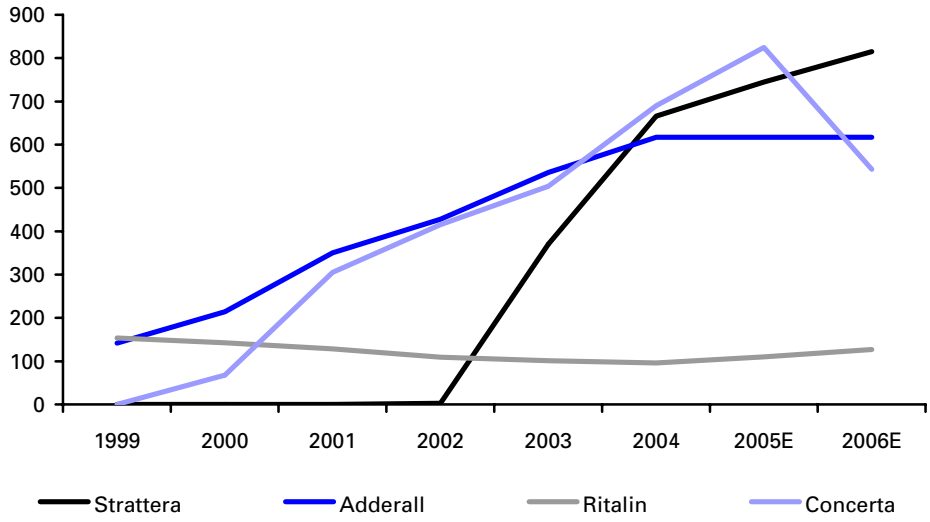
Also in development is what could become the first objective diagnostic test for ADHD. Based on research that has revealed two- to four-fold greater dopamine transporter density in clinically diagnosed ADHD patients, Boston Life Sciences created an imaging agent, Altropane, which enables detection of abnormal dopamine transporter levels via SPECT imaging scans. However, the fact that it utilises a radioactive isotope to measure dopamine transporter levels will likely limit its potential – especially in the paediatric population.

Figure 247: Key pipeline drugs for ADHD

Name	Sponsor	Description	Status	Est filing
Methypatch	Shire	Methylphenidate transdermal patch	Launch 2005	Filed
SPD503	Shire	Non-stimulant, non-scheduled	Phase III	2005
SPD465	Shire	Long-acting mixed amphetamines	Phase III	2005
NRP104	Shire/New River	Amphetamine prodrug	Phase III	2005

Source: Deutsche Bank

Figure 248: Sales growth of leading ADHD drugs ($m)



Source: Company data, Deutsche Bank estimates

Figure 249: Sales growth of leading ADHD drugs ($m)

		1999	2000	2001	2002	2003	2004	2005E	2006E
Strattera	Eli Lilly	0	0	0	3	370	666	745	815
Adderall	Shire	142	214	350	428	536	617	617	617
Ritalin	Novartis	154	143	128	110	101	96	110	127
Concerta	J&J	0	68	305	415	504	690	825	543

Source: Deutsche Bank

Migraine

- World triptan market in 2004 worth roughly $2.2bn
- Overall growth estimated at 4% per annum
- Growth driven by DTC advertising and earlier treatment
- Leading products are the triptans, of which GSK's Imitrex has the leading share

Migraine is a common condition affecting 10-15% of the population. Sufferers experience blinding headaches and nausea that can last several hours. Ten percent of patients suffer from the classical definition of migraine, with visual disturbances (aura), such as white flashing lights or distorted view of objects seen prior to the onset of the headaches. These disturbances enable physicians to easily diagnose the disease and prescribe the necessary medicine. The majority of migraine sufferers (approximately 85%), however, do not experience an initial aura. Consequently, they are harder for physicians to diagnose and do not often receive the required medicine.

Physiology

Migraine can be set off by a number of stimuli. These include diet, menstruation, stress and medications. The exact mechanism by which migraine occurs is currently unknown. However, a number of hypotheses have been put forward, the main one being based on the concept of an abnormal neuronal discharge followed by constriction of the blood vessels in the brain. This is illustrated in Figure 250.

This mechanism suggests that migraine starts with a neuronal disturbance, possibly caused by the stimuli outlined above. This leads to hyperactivity of nerve cells in an area of the brain where it meets the spinal cord and the release of large amounts of neuropeptides, namely noradrenalin and serotonin (5-HT). These neuropeptides cause the blood vessels in the brain to narrow (intra-cerebral vasoconstriction), resulting in a number of visual disturbances being experienced by the patient.

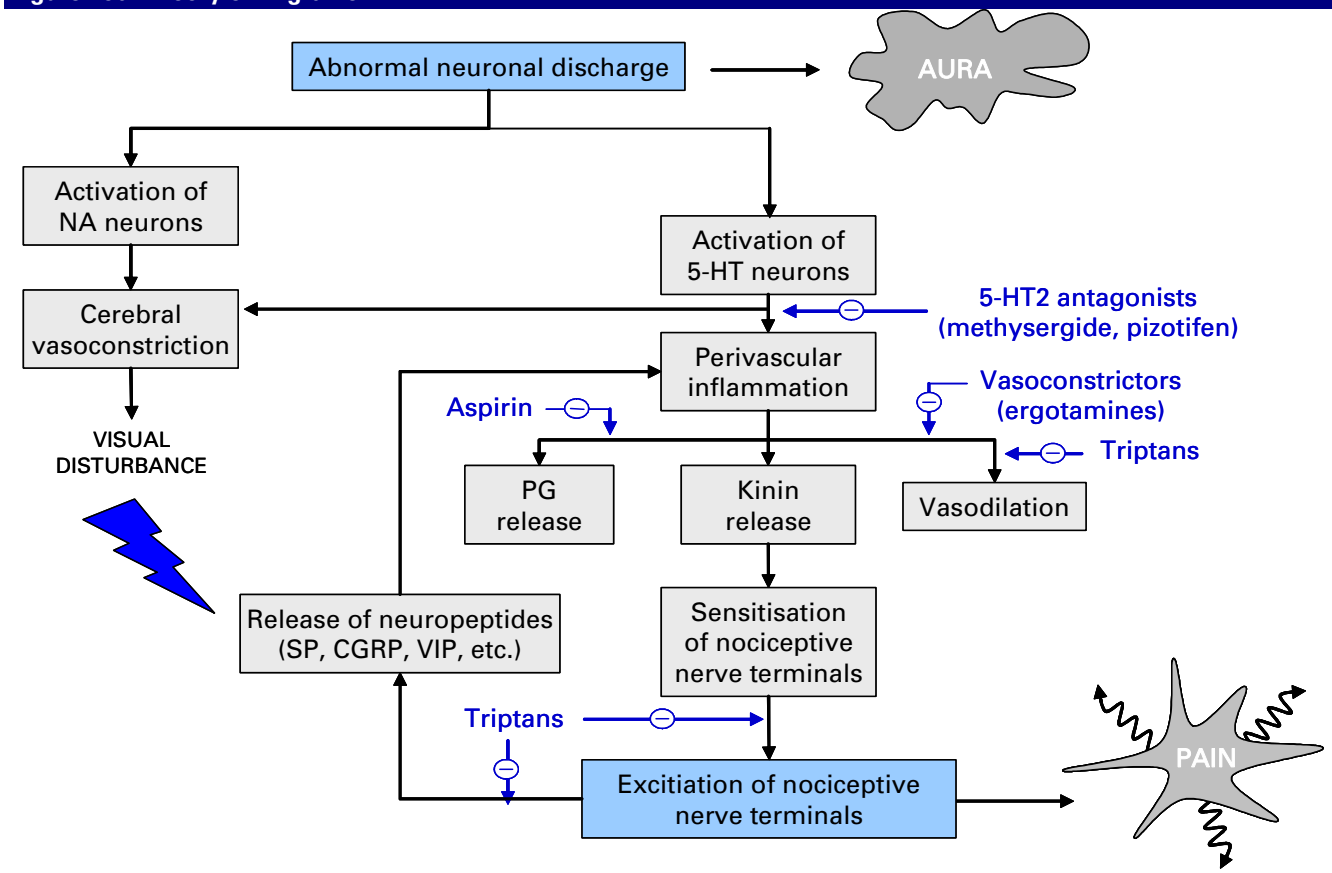
The 5-HT released is also postulated to act on blood vessels outside the brain, including the lining of the brain (the meninges), leading to local inflammation and subsequent expansion of the blood vessels (vasodilation). It is postulated that it is the impact on pain receptors in these regions that leads to the subsequent 'blinding headache' that is the main symptom of a migraine attack.

Pharmacological treatment

A range of treatments is available to treat migraine, depending upon the seriousness of the condition.

- **Mild to moderate cases** are treated using over-the-counter medicines such as:
  - **Simple analgesics,** including aspirin, which act to restrict the release of prostaglandins, thereby reducing, but not completely eradicating the pain experienced; and
  - **Non-steroidal anti-inflammatory drugs,** (NSAIDs) such as ibuprofen, which reduce the level of inflammation seen outside the brain and subsequently, vasodilation and pain.

Figure 250: Theory of migraine



Source: Rang, Dale & Ritter

- **Moderate to severe cases** are treated with prescription medicines that include:
  - the older **ergotamines** (vasoconstrictors), which as 5-HT1 antagonists inhibit the presynaptic activities that lead to pain; and
  - the newer **triptans,** for example, GlaxoSmithKline's Imitrex (sumatriptan), which specifically target the 5-HT1D receptors believed to be responsible for vasodilation and pain. The drugs initiate vasoconstriction and thus bring about pain relief. This group of drugs now accounts for over 90% of retail migraine prescriptions in the US.

Imitrex was the first triptan on the market. Launched in 1993, it continues to command over 50% market share due to its high efficacy. Other triptans have been launched between 1997 and 2003, but these have only led to modest additional market expansion. Given that an estimated 10-15% of the developed world's population suffer from migraine, the 5% p.a. growth of the class is somewhat disappointing. Surveys conducted in the US showed that only one in ten patients receives the correct treatment and that 50% of those who have migraine do not know it. One reason for this is that the vast majority of patients who do not suffer the classical aura may be incorrectly diagnosed. Consequently, there remains a significant market potential in this indication; however, as yet there is little evidence that the pharmaceutical sector is making headway in penetrating this opportunity.

Figure 251: Summary of key triptans

Brand name	Generic name	Producer	2004 Sales
Imitrex/Imigran	sumatriptan	GlaxoSmithKline	$1.2bn
Naramig/Amerge	naratriptan	GlaxoSmithKline	$0.2bn
Zomig	zolmitriptan	AstraZeneca	$0.4bn
Maxalt	rizatriptan	Merck	$0.3bn
Frova	frovatriptan	Elan	<$0.1bn
Relpax	eletriptan	Pfizer	$0.2bn

Source: Company data

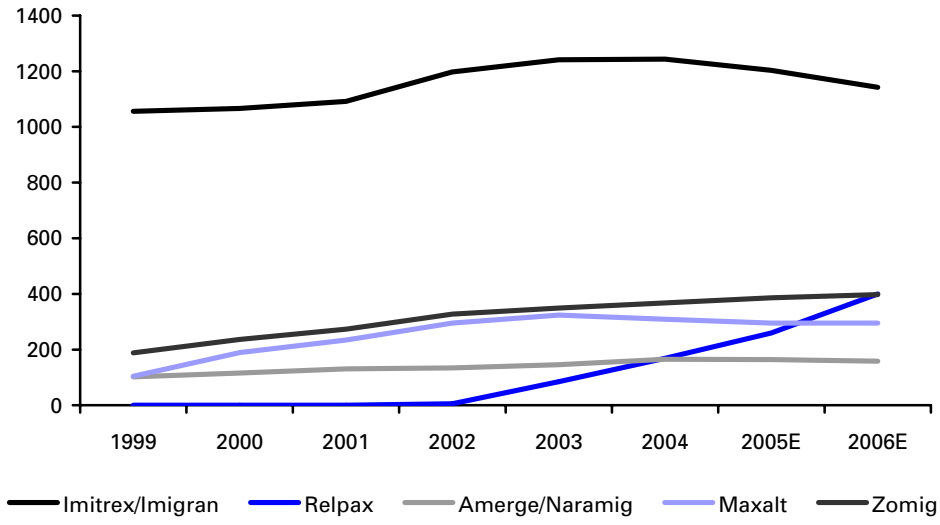
Clinical end-points

Clinical end-points are defined as the relief of moderate or severe pain to no or mild pain without the use of additional medication after a set time period (typically two or four hours).

Pipeline products

Given the modest growth of the category together with the strong efficacy and safety profile of the triptans, there is little of note in the pipeline. However, GSK is aiming to improve upon its market-leading triptan Imitrex with a combination product, Trexima. Trexima combines the active ingredient in Imitrex (sumatriptan) with the NSAID naproxen and is designed to offer best-in-class potency together with a faster onset of action than Imitrex.

Figure 252: Sales forecast for leading triptans ($m)



Source: Company data, Deutsche Bank estimates

Figure 253: Sales forecast for leading triptans ($m)

		1999	2000	2001	2002	2003	2004	2005E	2006E
Imitrex/Imigran	GlaxoSmithKline	1056	1067	1092	1198	1241	1244	1203	1143
Relpax	Pfizer	0	0	0	6	85	169	260	400
Amerge/Naramig	GlaxoSmithKline	102	117	131	135	146	166	164	159
Maxalt	Merck	105	190	235	295	324	309	295	295
Zomig	AstraZeneca	189	237	273	328	349	368	387	398

Source: Deutsche Bank

NOTES

Oncology

- World market approaching $28bn in 2004
- Growth estimated at upwards of 15% p.a. driven by ageing population and novel agents
- Leading players include AstraZeneca, Novartis and Roche

Cancer is one of the major causes of death in the developed world. Roughly one in five people will die from some form of cancer, while one in three will suffer from a cancer at some point in their lives. Sadly, because the disease is largely prevalent in older age groups, its incidence is rising. There are many types of cancer. However, as yet, there is no known cure for the disease, although some types are now well controlled.

Cancer (also called a tumour or neoplasm) is a disease in which the body's cells divide and multiply in an uncontrolled manner. In addition, whereas normal cells do not migrate to other parts of the body, malignant or 'metastatic' cancer cells are invasive and able to travel via the blood or lymphatic system and multiply elsewhere. Thus, a metastatic cancer is one that can spread in an uncontrolled manner. For example, in metastatic breast cancer, breast cells that would normally be unable to develop outside the breasts spread to other organs. This makes the disease all the harder to treat. By contrast, if a tumour is benign, it does not have the potential to migrate or metastasise.

Sadly, the treatment of cancer is still very crude. The first line of clinical treatment is typically surgical removal of the cancerous area. This may be accompanied by irradiation and chemotherapy, the role of each depending upon the type of cancer. Additionally, because the central objective of chemotherapy is to kill human cells, chemotherapy is often blunt and crude. All too frequently it is also ineffectual.

The biology of cancer

The division and multiplication of human cells is controlled by several factors. The body releases various growth messengers called cyclins and cyclin-dependent kinases that bind to cell receptors and stimulate a cell to start dividing. Genes called proto-oncogenes located on human DNA (for example, the *ras* gene), control the production of these messengers and the production of their cell receptors. At the same time, these growth-initiating messengers are regulated by several negative feedback mechanisms. Proteins are produced that can bind to the growth messengers and inhibit their action. These proteins are also encoded for by various genes, in particular, the tumour suppressor gene p53 and the Rb gene. In effect, these genes act as brakes on the replication system.

Once the new process is initiated, the cell's DNA is replicated and the proteins required to create a new cell are produced. Importantly, the process of cell replication includes checks and balances designed to ensure accuracy. Not least among these is the action of the *p53* gene, which, if the DNA is damaged, encourages cell self-destruction (apoptosis).

In cancer cells, an inherited or acquired mutation has occurred in the normal cell's DNA. Mutation is generally a multi-stage process which may be caused by, for example, exposure to a DNA-corrupting substance or viral damage. However, the end result of the process is normally one of the following changes:

- The tumour suppressor genes (*p53* and so on) are inactivated. Mutations in p53 are the most common mutations found in human cancer cells.
- The proto-oncogenes that produce growth messengers and receptors and so on become overactive and become oncogenes. In 20-30% of all cancers, the *ras* gene has mutated.

Principles of chemotherapy

The basic principle of chemotherapy is similar to that of antibiotics. The objective of treatment is clearly to kill the cancer cells, but leave the normal cells unchanged. However, the challenge in cancer is that both cells are human and therefore are common in almost every respect. Thus, unless differences in mechanism or cell nature can be found, it is impossible to be cancer-cell specific.

One key difference does, however, exist between cancer cells and normal cells. Cancer cells tend to divide more rapidly than most normal cells. Thus, most cytotoxic agents target the process of replication, as this will have the greatest impact on rapidly dividing cells. Sadly, however, not every normal cell divides slowly. Some, such as bone marrow, hair, those lining the intestine, reproductive cells, and so on, also divide rapidly. Consequently, it is in these organs that the most significant side effects of chemotherapy are often seen.

Of course, what would be ideal would be to find a specific and differentiating site on the cancer cell that could be targeted, and it is this approach to cancer chemotherapy that has driven the development of many monoclonal antibody-based drugs. Monoclonal antibodies (mAbs) are antibodies to a particular protein which are genetically replicated using cloning techniques. By attaching a toxin or radio-isotope to an antibody that is specific to a cancer cell, the cancer cell can be targeted. Another approach has been to disrupt the blood vessels that the cancer creates and needs to grow, that is, interfere with cell proteins called metalloproteinases that enable the creation of new blood vessels (angiogenesis). As the products of the biotechnology revolution of the 1980s make their way through the clinical process, drugs of this nature are playing an increasingly large role in cancer therapy.

Drugs used to treat cancer

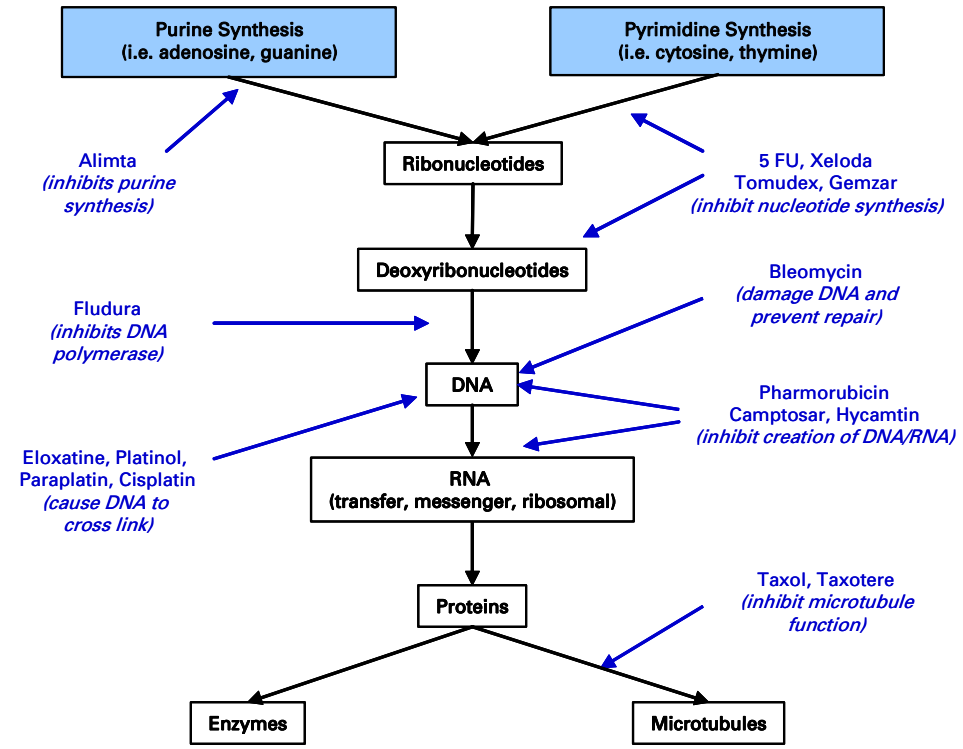
Cancer drugs may be classified by mechanism or alternatively by indication. Over the following pages, we discuss the common biological pathways, while in the subsequent sections, we highlight the therapeutic applications of these products.

Mechanistically, cancer drugs can be broadly spilt into three classes: cytotoxics, hormonals and the newer targeted therapies. Cytotoxic drugs tend to work by interfering with the process of DNA replication or cell division. By contrast, hormonal therapy is aimed at blocking hormone-sensitive receptors that play a key role in promoting cell growth. Targeted therapies include drugs such as the monoclonal antibodies described above. Cytotoxic drugs represent the major category, with 2004 sales of $9bn. Hormonal drugs achieved sales of $6bn, while targeted drugs represent the fastest growing class with 2004 sales of approximately $7bn.

Cytotoxic drugs

Most cytotoxic drugs seek to damage the cell's DNA and trigger cell death or apoptosis, the theory being that the cell's self-destruct mechanism is still intact. Many of these drugs cause DNA to cross-link. Alternatively, they attempt to corrupt the constituents of DNA itself (i.e. the purines and pyrimidines – adenosine, guanine, thymidine and cytosine – which come together to form base pairs). However, for apoptosis to occur, the p53 gene must be unaffected and, as we have stated, mutation of this gene is common in cancerous cells. Other drugs such as the taxanes (Bristol-Myers Taxol and Sanofi-Aventis' Taxotere) attempt to inhibit cell division (mitosis) by blocking microtubule formation.

Figure 254: Mechanisms of action of key cytotoxic drugs



Source: Rang, Dale & Ritter

The diagram above depicts the stages of cell division and the key action points of some of the more important cytotoxic drugs. Overall, these drugs can largely be divided into several main categories:

- **Alkylating agents,** which act by forming covalent bonds between DNA, so impeding replication. This category includes drugs such as the platinum compounds (e.g. Paraplatin, Platinol and Eloxatine).
- **Antimetabolites,** which block or subvert the production of DNA, often by interfering with purine and pyrimidine synthesis. Drugs that work in this manner include methotrexate, 5-fluorouracil (5-FU), Xeloda and Gemzar.
- **Cytotoxic antibiotics,** which prevent mammalian cell division by degrading DNA or inhibiting DNA synthesis. The most frequently used of these are bleomycin and doxorubicin.
- **Plant derivatives,** such as the taxanes and vinca alkaloids, which disrupt cell division. This category includes products such as Taxotere and Taxol.

Side effects and resistance

One of the main disadvantages of all cytotoxic drugs is that by their very nature they cause damage to normal cells. Thus side effects are a major disadvantage in their use. Typically, cytotoxic drugs cause kidney and nerve damage, largely because of the damaging impact of their metabolites, as well as nausea and negative effects on other fast-dividing cells (such as hair follicles). Most significant here is their effect on the immune system, which can be substantially depleted as white blood cells (lymphocytes) are damaged, leaving the patient vulnerable to infection.

Beyond side effects, resistance to treatment is also a problem. Resistance can be primary (that is, present when the drug is first given) or acquired as cancer cells adapt. Consequently, cytotoxic agents are often used in combination. Intermittent large doses are also often more effective than smaller regular doses to which resistance can build.

Figure 255: Leading branded cytotoxics

Brand	Generic	Producer	2004 sales	Mechanism
Taxol	paclitaxel	Bristol-Myers Squibb	$1.0bn	Prevents cell division
Taxotere	docetaxel	Sanofi-Aventis	$1.8bn	Prevents cell division
Gemzar	gemcitabine	Eli Lilly	$1.2bn	Inhibits DNA synthesis
Paraplatin	carboplatin	Bristol-Myers Squibb	$0.7bn	Causes DNA crosslinking
Camptosar	irinotecan	Pfizer	$0.8bn	Interferes with topoisomerase I
Eloxatin	oxaliplatin	Sanofi-Aventis	$1.5bn	Causes DNA crosslinking
Pharmorubicin/Ellence	epirubicin	Pfizer	$0.3bn	Inhibits DNA and RNA synthesis
Xeloda	capecitabine	Roche	$0.4bn	Inhibits DNA and RNA synthesis
Temodar	temozolomide	Schering-Plough	$0.6bn	Causes DNA alkylation
Alimta	pemetrexed	Eli Lilly	launch	Inhibits purine synthesis

Source: Company data

Hormonal therapy

In certain cancers, hormones play a major role in promoting cell growth. Most significant here are breast and prostate cancer, where the hormones oestrogen and testosterone play important roles in cell proliferation. Consequently, drugs have been developed that seek to interfere with these pathways, by either reducing oestrogen production in breast cancer or testosterone production in prostate cancer.

There are essentially four different types of hormonal therapy, each of which is directed at either reducing the production of the relevant hormone or blocking its action upon cell receptors. The different types of therapy are described overleaf.

Anti-oestrogens

Drugs in this class, such as AstraZeneca's Nolvadex (tamoxifen), interfere with oestrogen's ability to bind to cell receptors or deplete the number of receptors. In addition to its use in the treatment of advanced or metastatic breast cancer, Nolvadex has also for many years been the standard of care in the adjuvant (i.e. post-surgery) setting.

Figure 256: Leading anti-oestrogens

Brand	Generic	Producer	Sales 2004
Nolvadex	tamoxifen	AstraZeneca	$0.1bn
Faslodex	fulvestrant	AstraZeneca	$0.1bn

Source: Company data

Aromatase inhibitors

Aromatase is an enzyme that plays an active role in the production of oestrogen from cholesterol. By interfering with this enzyme, the aromatase inhibitors aim to block the production of oestrogen. Based on an increasing body of clinical data, the aromatase inhibitors are gradually replacing tamoxifen as the standard of care for the treatment of both metastatic and adjuvant breast cancer.

Figure 257: Leading aromatase inhibitors

Brand	Generic	Producer	Sales 2004
Arimidex	anastrozole	AstraZeneca	$0.8bn
Femara	letrozole	Novartis	$0.4bn
Aromasin	exemestane	Pfizer	$0.1bn

Source: Company data

Anti-androgens

The anti-androgens act by either blocking the production of testosterone from cholesterol in the testes or blocking the action of testosterone metabolites on cell receptors, thereby preventing cell division.

Figure 258: Leading anti-androgens

Brand	Generic	Producer	Sales 2004
Casodex	bicalutamide	AstraZeneca	$1.0bn
Eulexin	flutamide	Schering-Plough	<$0.1bn
Androcur (Europe only)	cyproterone	Schering	$0.1bn

Source: Company data

Luteinising hormone-releasing hormone (LHRH) analogues

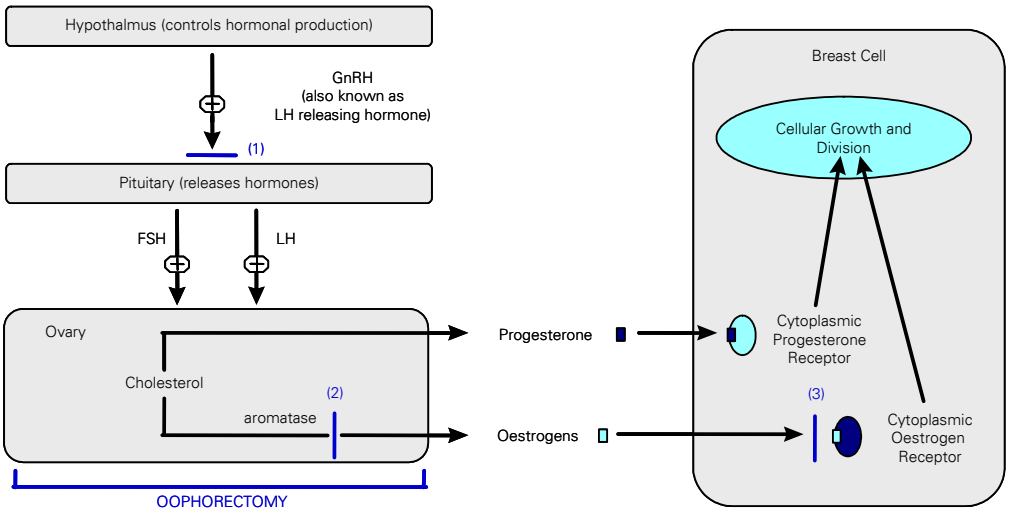
Oestrogen, progesterone and testosterone production is under the control of the hypothalamus, a major hormone-controlling gland located in the brain. The LHRH analogues (also known as gonadotropin releasing hormone or GnRH analogues) inhibit the production of luteinising hormone (LH) and with it, the subsequent production of the main sex hormones.

Figure 259: Leading LHRH analogues

Brand	Generic	Producer	Sales 2004
Zoladex	goserelin	AstraZeneca	$0.9bn
Lupron	leuprolide	Takeda Abbot Pharmaceuticals	$1.5bn
Eligard	leuprolide	Sanofi-Aventis	$0.1bn

Source: Company data

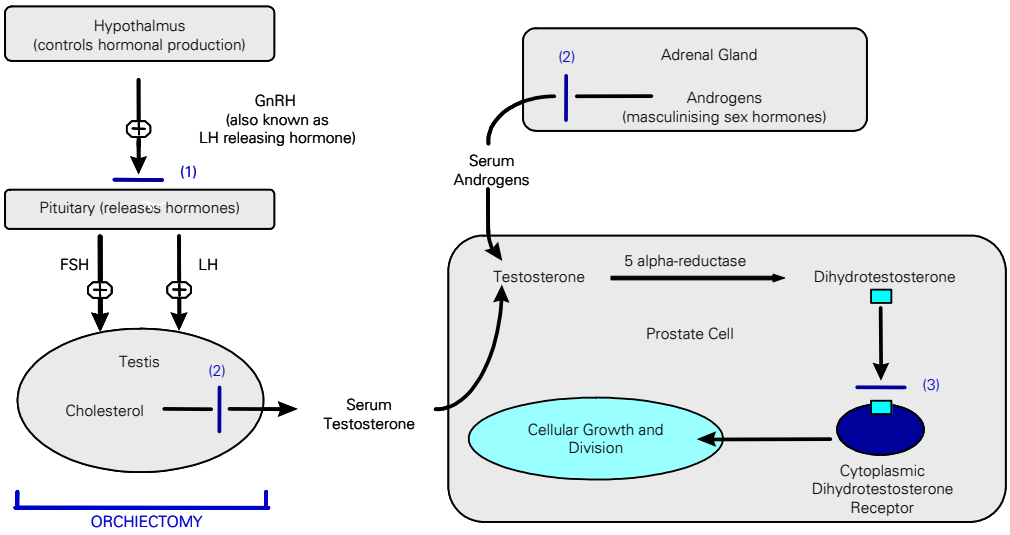
Figure 260: Hormonal regulation and breast cancer



Source: Rang, Dale & Ritter

As illustrated in Figure 260, in breast cancer LHRH analogues interfere with the production of sex hormones at position 1 by dampening the action of LH releasing hormone on the pituitary. Further along the pathway, aromatase inhibitors act to prevent the conversion of cholesterol to oestrogen. Finally, anti-oestrogens act within the breast cell itself at position 3, either by blocking the receptor or by depleting the number of receptors available.

Figure 261: Hormonal regulation and prostate cancer



Source: Rang, Dale & Ritter

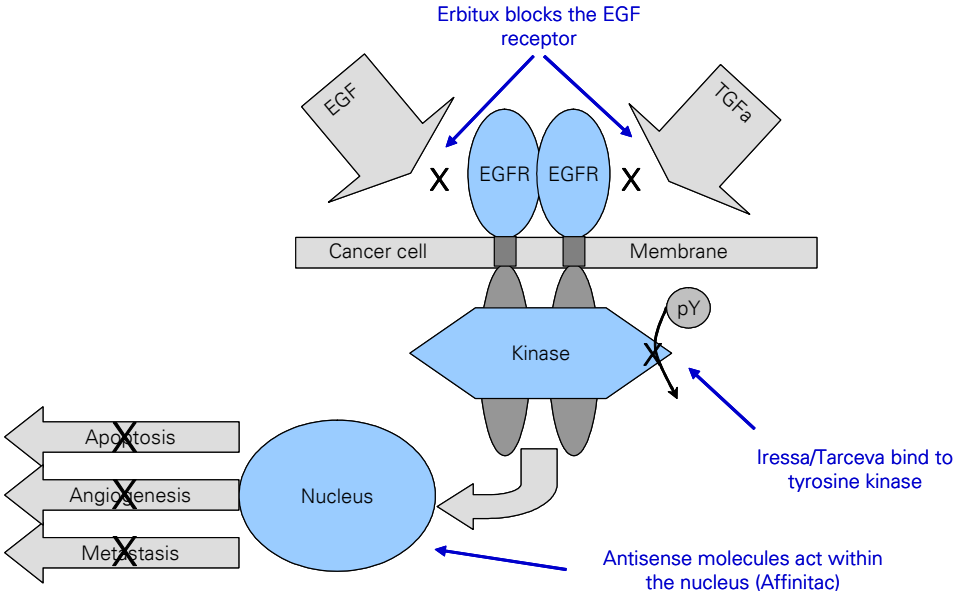
As with breast cancer, LHRH analogues can be used to dampen the impact of the hypothalamus on the pituitary in patients with prostate cancer. Subsequently, two types of anti-androgens are used, which play similar roles in prostate cancer to the aromatase inhibitors (by inhibiting the production of testosterone) and the anti-oestrogens, by blocking receptors promoting cell growth in the prostate gland itself.

Targeted therapy

Largely a product of the biotech industry, the newest and fastest-growing class of cancer drugs is the targeted therapies. Included in this class is Roche's blockbuster Mabthera/Rituxan, a genetically engineered antibody that binds to a specific antigen found on over 90% of non-Hodgkin's lymphoma (NHL) B-cells and facilitates cell death. Novartis' Gleevec, launched in 2001, is likewise a highly targeted therapy that has produced dramatic results in patients with chronic myeloid leukaemia (CML). Because these drugs employ more targeted approaches to attack cancer cells, they are often associated with less severe side effects than those seen with traditional cytotoxic drugs. However, this also implies that their application across different tumour types may be more limited, albeit this has clearly not hindered the potential of drugs such as Gleevec which generated sales of $1.6bn in 2004.

This class also represents the most significant area of new product development. Companies such as Roche and Bristol-Myers Squibb have recently launched drugs that target the receptor for epidermal growth factor (EGF), one of several hormones that functions as an essential communication messenger, instructing cells to stay alive, to proliferate, to become mobile, etc. The protein is over-expressed in a number of cancers, enabling unregulated replication and subsequent tissue invasion, metastasis, chemotherapy resistance and poor treatment outcomes. By targeting this protein, the EGFR inhibitors are designed to reduce tumour growth rather than destroy cancer cells.

Figure 262: Drug action points in EGFR-based cancer treatments



Source: AstraZeneca, EGFR-COM; EGF = epidermal growth factor, EGFR = EGF receptor, TGR = tissue growth factor, K = tyrosine kinase, Py = phosphorylation

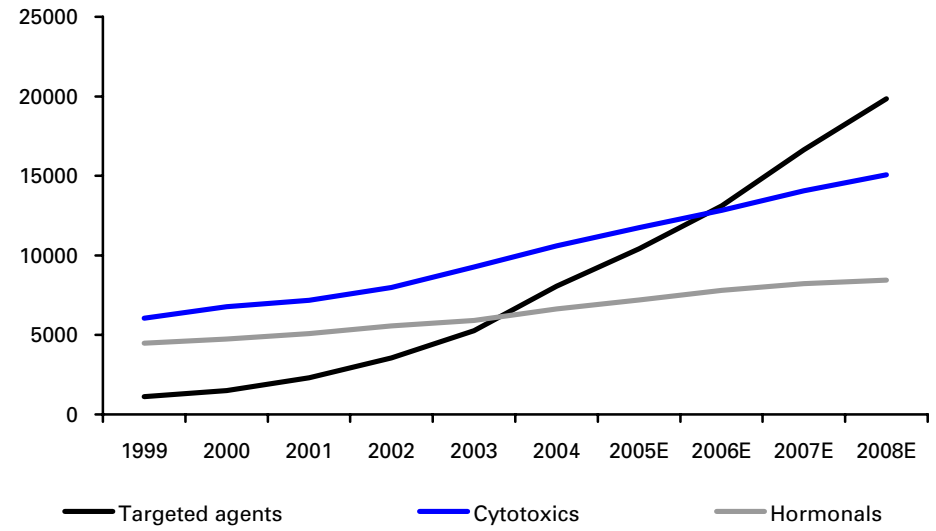
Roche and Genentech's targeted antibody, Avastin, is also rapidly becoming part of the first-line treatment paradigm for many solid tumour types. Avastin inhibits the vascular endothelial growth factor (VEGF), thereby interfering with cancer cells' ability to stimulate new blood vessel growth ("angiogenesis"), which is necessary to enable tumour expansion. To date, positive data have been presented in colorectal, breast and lung cancer with further development programmes ongoing. In light of the success of Avastin, a number of other companies are developing drugs that also target the VEGF pathway, but most are still several years away from reaching the market.

Figure 263: Key targeted cancer drugs

Brand	Generic	Producer	2004 sales	Mechanism (indication)
Mabthera/Rituxan	rituximab	Roche	$2.7bn	Anti-CD20 mAb (NHL)
Herceptin	trastuzumab	Roche	$1.2bn	Anti-HER2 mAb (breast cancer)
Glivec/Gleevec	imitinib	Novartis	$1.6bn	Signal transduction inhibitor (CML, GIST)
Iressa	gefitinib	AstraZeneca	$0.4bn	EGFR inhibitor (NSCLC)
Erbitux	cetuximab	ImClone/BMS/Merck KGaA	$0.3bn	Anti-EGFR mAb (colorectal cancer)
Bexxar	tositumomab	GSK	<$0.1bn	I131 radiolabelled anti-B1 mAb (NHL)
Avastin	bevacizumab	Roche/Genentech	$0.6bn	Anti-VEGF mAb (colorectal cancer)
Tarceva	erlotinib	Roche	launch	EGFR inhibitor (NSCLC)

Source: Company data *NHL = non-Hodgkin's lymphoma; CML = chronic myeloid leukaemia; GIST = gastrointestinal stromal tumours; NSCLC = non-small cell lung cancer*

Figure 264: Sales growth of key classes of cancer drugs ($m)



Source: Wood Mackenzie

Figure 265: Sales growth of key classes of cancer drugs ($m)

	1999	2000	2001	2002	2003	2004	2005E	2006E	2007E	2008E
Targeted agents	1129	1509	2306	3562	5260	8068	10421	13110	16628	19843
Cytotoxics	6058	6771	7179	7984	9264	10604	11742	12826	14063	15059
Hormonals	4487	4746	5091	5578	5915	6635	7209	7804	8222	8438

Source: Wood Mackenzie

Supportive therapies

Due to the serious side effects caused by most cancer chemotherapies, there is a significant demand for drugs that help to alleviate these symptoms. These agents broadly fall into four categories: erythropoietins, cytokines, anti-emetics, and bisphosphonates. The erythropoietins (EPOs) are used for the treatment of chemotherapy-induced anaemia (red blood cell depletion) as well as anaemia associated with end-stage renal disease. Given that these agents account for upwards of $10bn in sales across all indications, we have devoted a subsequent chapter to their discussion. In the cytokine family, the key drugs include Amgen's Neupogen and its follow-on product Neulasta, both of which are indicated for the treatment of neutropenia (white blood cell depletion). Other products in this category include Neumega for the treatment of thrombocytopenia (platelet depletion). The anti-emetics, including GlaxoSmithKline's Zofran and Roche's Kytril, help treat chemotherapy-induced nausea. Finally, Novartis' Zometa and others comprise the injectable bisphosphonate class for the treatment and prevention of bone metastases.

Figure 266: Key supportive therapies (excluding EPOs)

Brand	Generic	Company	Indication	2004 Sales
Neupogen	filgrastim	Amgen	Neutropaenia	$1.2bn
Neulasta	pegfilgrastim	Amgen	Neutropaenia	$1.7bn
Neutrogin	filgrastim	Roche	Neutropaenia	$0.3bn
Leukine	sargramostim	Schering	Neutropaenia	$0.1bn
Kytril	granisetron	Roche	Emesis	$0.4bn
Zofran	ondansetron	GlaxoSmithKline	Emesis	$1.4bn
Aloxi	palonosetron	MGI Pharma	Emesis	$0.2bn
Emend	aprepitant	Merck	Emesis	$0.1bn
Zometa	zoledronate	Novartis	Bone metasteses	$1.1.bn
Bondronat	ibandronate	Roche	Bone metasteses	<$0.1bn
Bonefos	clodronate	Schering	Bone metasteses	<$0.1bn

Source: Deutsche Bank

Clinicians' approach to cancer

As a final comment, it is worth noting that because cancer is often fatal, oncologists are willing to try many different drugs, often in combination with each other. Where there is little hope of recovery, the objective of treatment is often purely to defer the day of reckoning without significantly reducing the patient's quality of life. Drugs will be recommended for first-, second- or third-line treatment, depending upon their rate of success relative to other compounds and the impact that they have on a patient's wellbeing or quality of life. It should also be appreciated that because doctors are dealing with patients who are likely to die, cancer drugs are frequently used off-label, that is, anything will do, provided it offers some hope of recovery or defers the day of reckoning. Thus, if clinicians are aware that a drug undergoing trials has shown some degree of efficacy, they will often try it in relevant patient groups, even if regulatory approval has not yet been granted.

Drug treatment by cancer type

Over the following pages, we discuss treatment guidelines for the four main types of cancer, including prostate, breast, lung and colorectal. However, for reference, a broader summary of cancer types, including incidence and survival rates, is shown below.

Figure 267: Incidence, death and survival rates for key cancer types

			---------- 5-year Survival ----------		
Cancer type	New cases*	Deaths*	Localised	Distant	Overall
Prostate	232,090	30,350	100%	34%	96%
Breast	211,240	40,410	96%	21%	86%
Lung	172,570	163,510	48%	3%	15%
Colorectal	145,290	56,290	90%	10%	61%
Bladder	62,310	13,180	94%	6%	83%
Melanoma	59,580	7,770	96%	13%	89%
Non-Hodgkin's lymphoma	56,390	19,200	>75%	30%	59%
Renal cell carcinoma	36,160	12,660	90%	9%	60%
Pancreatic	32,180	31,800	15%	n/a	4%
Ovarian	22,200	16,210	90%	20%	44%
Esophageal	14,250	13,300	27%	5%	14%
Cervical	10,370	3,710	92%	20%	71%

Source: Amercian Cancer Society **Estimates for 2005*

In general, chemotherapy falls into two categories depending on the stage of the patient's disease:

- **Early-stage** – The first course of treatment for most cancers is surgical removal of the tumour. However, to enhance the patient's chances that the surgery will be successful and that the cancer will not recur, patients often receive cancer drugs before or after surgery. Depending on whether drugs are administered pre- or post-surgery, this is called 'neoadjuvant' or 'adjuvant' treatment.
- **Metastatic** – In advanced stage cancer patients where the tumour is inoperable and/or it has spread to other parts of the body, treatment relies on radiation and/or chemotherapy. Typically, two or more chemotherapy regimens will ultimately be used as the patient fails on the first-line treatment and moves to the second-line option and so forth.

The relative size of these categories varies from one type of cancer to the next. In breast cancer, for example, where tumours are often recognised early, the adjuvant market may be twice the size of that for metastatic disease, whereas in lung cancer, the metastatic market accounts for the lion's share of drug use.

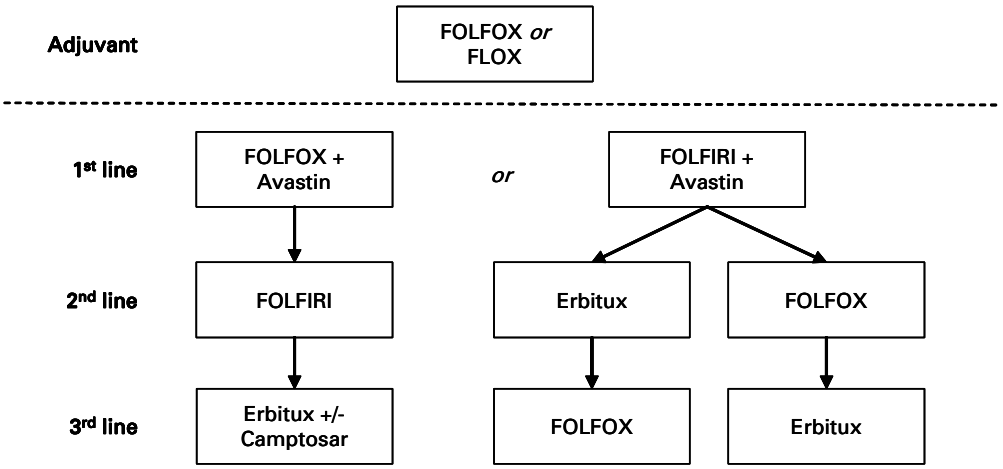
Colorectal cancer

Colorectal cancer (CRC) currently represents the third leading cause of cancer-related deaths in the US. As the name suggests, this type of cancer comprises tumours that develop either in the colon (also known as the large intestine) or the rectum. Ninety-five percent of colorectal tumours are adenocarcinomas, meaning that they develop from glandular cells that line the inside wall of the colon and rectum. However, less common tumours that may occur in this region include gastrointestinal stromal tumours (GIST), which develop from specialised cells ("interstitial cells of Cajal") found in the wall of the colon, and carcinoid tumours which develop from hormone-producing cells of the intestine.

The relative survival for CRC patients whose cancer has been treated at an early stage is 90%. However, only 39% of tumours are diagnosed at this stage, and once the cancer has spread to the nearby organs or lymph nodes, the 5-year survival rate falls to 67%. If the cancer has spread to distant organs and lymph nodes, the survival rate is only 10%.

The primary drugs and drug regimens to treat CRC are shown below. In the metastatic setting, there are two alternative first-line regimens that are used fairly equally. These are referred to by clinicians as FOLFOX (Eloxatin + 5-fluorouracil + leucovorin) and FOLFIRI (Camptosar + 5-fluorouracil + leucovorin). However, the choice of one first-line treatment over the other will imply a different course of second- and third-line options. In the adjuvant setting the story is slightly different, as Eloxatin has demonstrated an impressive survival benefit (>20% reduction in the risk of cancer recurrence), whereas Camptosar has consistently failed to show significant activity in this indication.

Figure 268: Treatment paradigm for colorectal cancer



Source: Deutsche Bank
FOLFOX = infusional Eloxatine + 5-FU + leucovorin; FLOX = bolus Eloxatine + 5-FU + leucovorin; FOLFIRI = infusional Camptosar + 5-FU + leucovorin

Figure 269: Leading drugs for the treatment of colorectal cancer

Drug	Generic	Adjuvant	1st line	2nd line	3rd line	Comment
Eloxatin	oxaliplatin	x	x	x		FOLFOX = infusional 5FU/LV + oxaliplatin
Camptosar	irinotecan		x	x		FOLFIRI = infusional 5FU/LV + irinotecan; IFL or 'Saltz' regimen = bolus 5FU/LV + irinotecan; No survival benefit seen in adjuvant setting
Avastin	bevacizumab		x	(x)		Positive data reported in combination with FOLFOX in 2nd line
Erbitux	cetuximab				x	Approved as single agent or in combination with irinotecan
Xeloda	capecitabine	x	x			May substitute for 5-FU/leucovorin; XELOX = capecitabine + oxaliplatin

Source: Deutsche Bank (x) - Regulatory filing/approval anticipated within 12-18 months

NOTES

Lung cancer

Lung cancer is the second most common type of cancer found in both males and females and is by far the leading cause of cancer-related death. Non-small cell lung cancer (NSCLC) accounts for around 87% of all cases, with the balance caused by small cell lung cancer (SCLC). SCLC cases are often widespread by the time of diagnosis such that treatment is limited to chemotherapy and/or radiation. However, NSCLC is often caught early enough such that surgical resection may be possible.

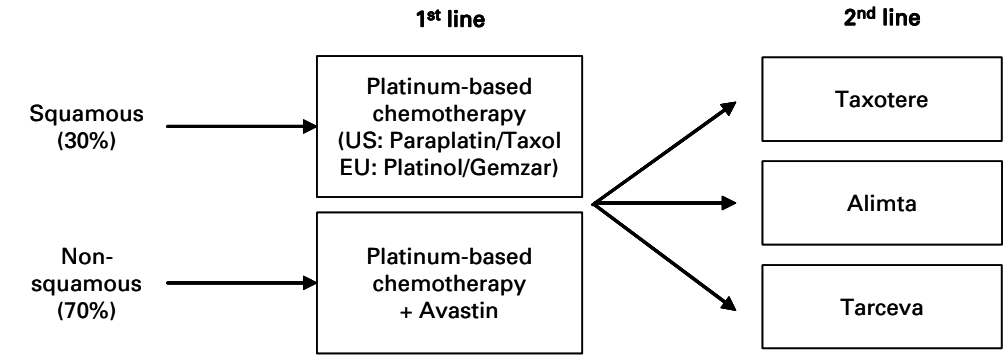
In NSCLC, the following subtypes account for the majority of all tumours:

- **Squamous cell carcinomas** – These account for around 30% of NSCLC cases and are often centrally located. They are generally associated with a history of smoking and tend to be slow growing.
- **Adenocarcinomas** – These account for 40% of NSCLC cases and are usually found on the periphery of the lungs. Adenocarcinomas typically have a worse prognosis than squamous cell tumours.
- **Other non-squamous cancers** – These account for the remainder of cases and include, amongst others, large cell cancer.

Nearly 60% of people diagnosed with lung cancer will die within one year and 75% will die within two years. For patients whose tumour is diagnosed before it has spread, the 5-year survival rate is roughly 49%. However, only 16% of patients are diagnosed at this stage, and the 5-year survival rate across all patients is 15%.

The primary drug regimens used to treat NSCLC are shown below. Given the small number of patients diagnosed at an early stage and the lack of conclusive data supporting adjuvant treatment, the focus of chemotherapy is in the metastatic setting. First-line treatment generally relies on a platinum-based compound together with another cytotoxic agent, often in combination with radiation therapy. However, the preferred combination of drugs differs in the US and Europe, with American oncologists preferring the combination of Paraplatin and Taxol whereas European clinicians tend to use Platinol and Gemzar. In addition, we expect this paradigm to increasingly incorporate use of Avastin based on positive data presented at ASCO 2005, which showed a 2.3 month overall survival benefit for patients receiving Paraplatin/Taxol in combination with Avastin in the first-line setting. Treatment of SCLC also relies on platinum-based compounds, with Paraplatin or Platinol in combination with etoposide being the most commonly used regimen.

Figure 270: Treatment paradigm for NSCLC



Source: Deutsche Bank

Figure 271: Leading drugs in the treatment of lung cancer

		---------- NSCLC ----------				
Drug	**Generic**	**1st line**	**2nd line**	**3rd line**	**SCLC**	**Comment**
Paraplatin*	carboplatin	x			x	
Platinol*	cisplatin	x			x	
Taxol*	paclitaxel	x				In combination with cisplatin
Taxotere	docetaxel	x	x			In combination with cisplatin in 1st line, and as single agent in 2nd line
Gemzar	gemcitabine	x				In combination with cisplatin
Alimta	pemetrexed		x			
Avastin	bevacizumab	(x)				Positive data reported for use in combination with paclitaxel/carboplatin in 1st line. Filing planned early 2006. Expected to become part of standard of care for patients with non-squamous tumours.
Tarceva	erlotinib		x			
Iressa	gefitinib			x		Failed to show survival benefit (ISEL study, Dec 2004)
Hycamtin	topotecan				x	

*Source: Deutsche Bank *Off-patent (x) - Regulatory filing/approval anticipated within 12-18 months*

Breast cancer

Excluding skin cancer, breast cancer is the most common cancer among women, with over one million new cases diagnosed worldwide each year. Fortunately, due to the increasing utilisation of mammograms and other screening techniques, most breast cancers are diagnosed at an early stage when the tumour is still highly operable and 'cure' rates are high. Frequent early detection also implies that the adjuvant (post-surgery) market accounts for the lion's share of drugs used in breast cancer. However, treatment decisions in both the adjuvant and advanced settings are complex and are dependent on the characteristics of the patient's tumour and various risk factors. We have attempted to summarise the most frequent treatment protocols in both of these settings below.

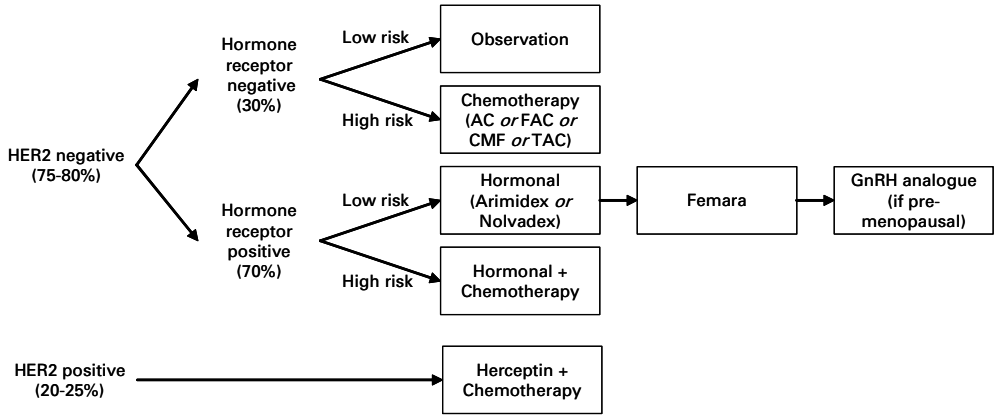
Adjuvant

Roughly 70% of patients diagnosed with breast cancer will be eligible for adjuvant drug therapy. For these patients, the choice of an appropriate drug regimen is primarily dependent on the patient's hormonal receptor status and whether she overexpress a protein known as HER2. In the case of patients who overexpress HER2, adjuvant treatment has historically relied on a course of chemotherapy as these patients were almost always considered high risk. However, in light of data presented at ASCO 2005, which showed a 50% reduction in the risk of cancer recurrence for patients receiving Herceptin, we expect chemotherapy plus Herceptin to become the new standard of care in this population.

Amongst patients who do not overexpress HER2, roughly two-thirds are likely to have tumours that are oestrogen and/or progesterone receptor positive ('ER-positive' or 'PR-positive'). In these patients, hormones are involved in the promotion of tumour growth, and thus treatment primarily relies on drugs that interfere with these hormonal pathways. Historically, a five-year course of AstraZeneca's Nolvadex (tamoxifen) was considered the first choice adjuvant treatment for hormone receptor-positive breast cancer patients. However, recent data have suggested that the aromatase inhibitors (e.g. Arimidex, Femara) offer an even greater reduction in the risk of cancer recurrence.

Finally, in patients who are hormone receptor-negative but who are at high risk of cancer recurrence (as well as in some of those who are hormone receptor-positive and high risk), physicians may prescribe a course of chemotherapy usually lasting 3-6 months. Traditionally, these have been doxorubicin-based regimens, with recent data supporting the addition of one of the taxanes (Taxol or Taxotere).

Figure 272: Treatment paradigm for adjuvant breast cancer



Source: Deutsche Bank AC = doxorubicin + cyclophosphamide; FAC = 5-FU + doxorubicin + cyclophosphamide; TAC = Taxotere + doxorubicin + cyclophosphamide; CMF = 5-FU + cyclophosphamide + methotrexate

Neoadjuvant

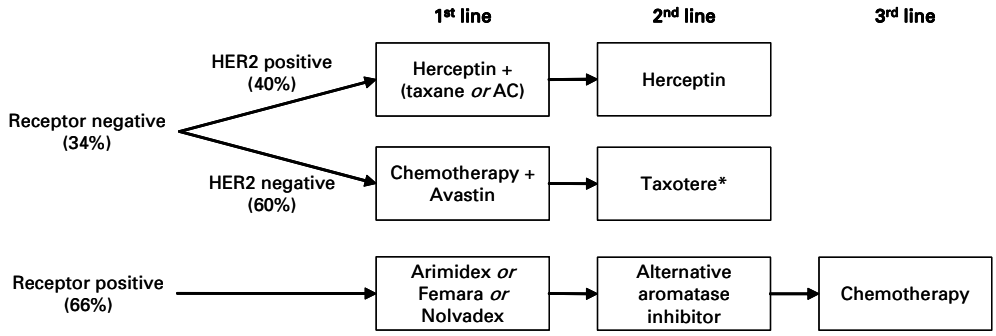
Additionally, there is data supporting the use of hormonal drugs (Nolvadex, Arimidex, Femara) and cytotoxics (AC, Taxotere) in the 'neoadjuvant' setting (i.e. before surgery). Administration of these drugs has been shown to shrink tumours ahead of surgery and increase the chances of allowing a breast-conserving procedure (i.e. lumpectomy versus mastectomy).

Metastatic

As in the adjuvant setting, treatment of metastatic breast cancer varies according to a number of factors including a patient's tumour type and disease prognosis. Patients who are receptor-positive may be treated with single agent hormonal therapy, while those who are receptor-negative will be eligible for chemotherapy. Importantly, hormonal therapy and chemotherapy are generally not combined in the metastatic setting, but the majority of patients on hormonal drugs will ultimately progress and move onto a cytotoxic regimen.

Additionally, some 25-30% of metastatic patients have tumours that overexpress HER2. These patients will receive Herceptin in combination with chemotherapy. However, Herceptin is currently only approved for first-line use in combination with chemotherapy and as a monotherapy for second-line patients. A clinical trial evaluating Herceptin in combination with hormonal therapy in metastatic patients should report in 2005.

Figure 273: Treatment paradigm for metastatic breast cancer



Source: Deutsche Bank **Taxane monotherapy approved as second-line treatment, but gaining usage in first-line setting.*

Figure 274: Leading drugs for the treatment of breast cancer

Drug	Generic	Adjuvant	1st line	2nd line	Comment
Taxol*	paclitaxel	x		x	In combination with doxorubicin-regimen in adjuvant. As single agent in 2nd line metastatic after failure on anthracycline regimen
Taxotere	docetaxel	x		x	In combination with AC in adjuvant. As single agent in 2nd line metastatic
Gemzar	gemcitabine		x		In combination with paclitaxel after failure of anthracycline-based adjuvant regimen.
Xeloda	capecitabine			x	In combination with docetaxel after failure of anthracycline-based regimen. As single agent in 3rd line after failure on paclitaxel and anthracycline-based regimen.
Ellence	epirubicin	x			In combination with cyclophosphamide and 5-FU
Nolvadex*	tamoxifen	x	x		Former gold standard for hormone-receptor positive tumours. Increasingly being displaced by aromatase inhibitors.
Arimidex	anastrazole	x	x	x	
Femara	letrozole	(x)	x	x	Approved in extended adjuvant setting (i.e. post 5-years tamoxifen). Positive interim data reported supporting use in adjuvant setting.
Aromasin	exemestane			x	Positive data reported in adjuvant setting when patients switched to exemestane after two years tamoxifen
Faslodex	fulvestrant			x	Following progression on anti-estrogen therapy
Zoladex	goserelin			x	Palliative treatment only
Herceptin	trastuzumab	(x)	x	x	In HER2 positive patients only. In combination with paclitaxel in 1st line. As single agent in 2nd line. Expected to become part of standard of care in adjuvant setting based on positive data presented at ASCO 2005.
Avastin	bevacizumab		(x)		Positive data in 1st line metastatic cancer presented at ASCO 2005.

Source: Deutsche Bank **Off-patent* *(x) - Regulatory filing/approval anticipated within 12-18 months*

Prostate cancer

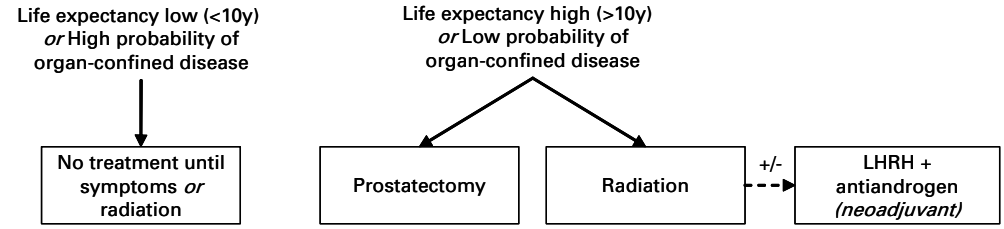
Prostate cancer is the most common cancer amongst American men. The disease is rare in men under the age of 40, but risk rises significantly with age. Fortunately, prostate cancer is often detected early through regular physical exams and screening for levels of a protein in the bloodstream known as prostate-specific antigen (PSA), which is typically seen at higher levels in patients with prostate cancer.

Early stage

Because prostate cancer often spreads very slowly and appears with advanced age, many men may never receive treatment for their condition. Given that the 10-year survival rate for localised tumours is over 80% and given the risks associated with treatment, doctors may opt for a period of 'watchful waiting'.

However, in the event the patient still has significant life expectancy (>10 years), the first course of treatment is a radical prostatectomy (removal of the prostate) or radiation therapy. A course of hormonal therapy using a luteinising hormone releasing hormone (LHRH) agonist together with an anti-androgen may also be used prior to and during radiotherapy to reduce the chance of disease recurrence. (Note that this combination is designed to achieve maximum androgen deprivation by blocking androgen production via the LHRH analogue and blocking androgen activity via the anti-androgen.) However, clinical data as yet have not shown a significant benefit associated with use of hormonal therapy following prostatectomy.

Figure 275: Treatment of early-stage, localised prostate cancer



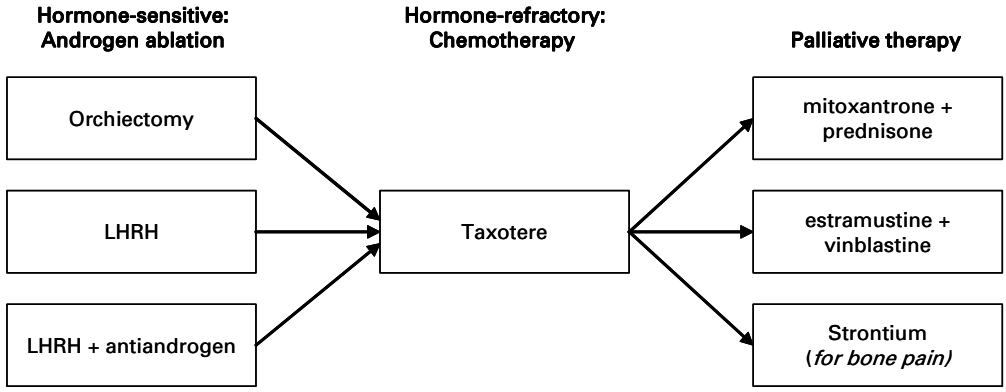
Source: Deutsche Bank

Metastatic

Although survival rates for patients with early stage prostate cancer are very high, some patients will develop advanced or metastatic disease. Traditionally, first-line therapy for these patients relies on androgen ablation via either an orchiectomy (surgical removal of the testes) or medical castration using an LHRH analogue, often in combination with an anti-androgen. While orchiectomy is arguably the more cost-efficient method, many patients prefer treatment with an LHRH analogue, as the surgical procedure is non-reversible and carries a significant psychological burden.

Unfortunately, while some 80% of patients respond to hormonal therapy, virtually all will eventually progress. Once all hormonal manipulations have been exhausted, the patient is considered to have hormone-refractory prostate cancer (HRPC). Until recently, all treatment options at this stage were merely palliative. However, Sanofi-Aventis recently reported the first positive survival data in this setting for Taxotere. In the landmark study presented in June 2004, Taxotere was shown to offer a 24% reduction in the risk of death compared to mitoxantrone. As the only chemotherapy drug with survival data in this setting, we expect Taxotere should soon become the new standard of care.

Figure 276: Treatment of metastatic prostate cancer



Source: Deutsche Bank

Figure 277: Leading drugs for the treatment of prostate cancer

Drug	Generic	Early-stage	Metastatic (hormone sensitive)	Metastatic (hormone refractory)	Comment
Lupron	leuprolide		x		
Eligard	leuprolide		x		
Zoladex	goserelin	x	x		
Plenaxis	abarelix		x		LHRH antagonist indicated only for patients not suitable for LHRH analogue therapy or orchiectomy due to risk of serious allergic reaction
Casodex	bicalutamide		x		
Eulexin*	flutamide	x	x		
Nilandron*	nilutamide		x		
Taxotere	docetaxel			x	First agent to improve survival in metastatic hormone refractory setting

Source: Deutsche Bank **Off-patent*

Pipeline drugs

Oncology is one of the biggest areas of focus for pharmaceutical R&D. Numerous drugs are in development that aim to improve upon existing products or are designed to offer new mechanisms to treat the disease. Major development projects are listed below according to cancer type.

Figure 278: Selected development candidates for colorectal cancer

Name	Sponsor	Class/Mechanism	Status	Est filing
PTK787	Schering/Novartis	VEGFR inhibitor	Phase III	TBD
ABX-EGF (panitumumab)	Amgen/Abgenix	Anti-EFGR mAb	Phase III	2006
LBQ707 (gimatecan)	Novartis	Topoisomerase I inhibitor	Phase II	>2007

Source: Deutsche Bank, Company information

Figure 279: Selected development candidates for non-small cell lung cancer

Name	Sponsor	Class/Mechanism	Status	Est filing
Avastin	Roche	Anti-VEGF mAb	Phase III	2006
vinflunine	Bristol-Myers Squibb	Vinca alkaloid	Phase III	2007
Zacrtima (ZD6474)	AstraZeneca	VEGFR inhibitor	Phase III	>2007
ABT-751	Abbott	Tubulin antagonist	Phase II	2007
715992	GlaxoSmithKline	KSP inhibitor	Phase II	>2007
MAC-321	Wyeth	Taxane	Phase II	>2007

Source: Deutsche Bank, Company information

Figure 280: Selected development candidates for breast cancer

Name	Sponsor	Class/Mechanism	Status	Est filing
ixabepilone	Bristol-Myers Squibb	Epothilone (tubulin inhibitor)	Phase III	2006
Avastin	Roche	Anti-VEGF mAb	Phase III	2006
temsirolimus	Wyeth	mTOR inhibitor	Phase III	2006
lapatinib	GlaxoSmithKline	Erb-B2 & EGFR inhibitor	Phase III	2006/7
MDX-010	BMS/Medarex	Anti-CTLA-4 mAb	Phase III	2006/7
XRP9881	Sanofi-Aventis	Taxane derivative	Phase III	>2007
RAD001	Novartis	mTOR inhibitor	Phase II	>2007
AG-13736	Pfizer	VEGFR inhibitor	Phase II	>2007

Source: Deutsche Bank, Company information

Figure 281: Selected development candidates for prostate cancer

Name	Sponsor	Class/Mechanism	Status	Est filing
Xinlay (atrasentan)	Abbott	Endothelin A receptor antagonist	Launch 2005	Filed
satraplatin	GPC Biotech	Platinum compound	Phase III	2006
ZD4054	AstraZeneca	Endothelin A receptor antagonist	Phase II	>2007
MDX-010	BMS/Medarex	Anti-CTLA-4 mAb	Phase II	>2007
ixabepilone	Bristol-Myers Squibb	Epothilone (tubulin inhibitor)	Phase II	>2007

Source: Deutsche Bank, Company information

Figure 282: Selected development candidates for other cancers

Name	Sponsor	Class/Mechanism	Status	Indication	Est filing
Zarnestra	Johnson & Johnson	Farnesyl transferase inhibitor	'Not approvable'	AML	Filed
BAY 43-9006	Bayer	Raf kinase inhibitor	Phase III	RCC	Filed
nelarabine	GlaxoSmithKline	Guanine arabinoside prodrug	Phase III	ALL	2005
MDX-010	BMS/Medarex	Anti-CTLA4 mAb	Phase III	Melanoma	2006
SAHA	Merck	Histone deacetylase inhibitor	Phase III	CTCL	2006
Sutent (SU-11248)	Pfizer	VEGFR, c-Kit inhibitor	Phase III	GIST, RCC	2005
tirapazamine	Sanofi-Aventis	Cytotoxic	Phase III	Head & neck	2007
BMS 354825	Bristol-Myers Squibb	SRC/ABL inhibitor	Phase II/III	CML	2007
enzastaurin	Lilly	PKC-beta inhibitor	Phase II/III	Glioblastoma	>2007
AMN107	Novartis	BCR-ABL inhibitor	Phase II	CML	>2007
CP-675,206	Pfizer	Anti-CTLA4R mAb	Phase II	Melanoma	>2007

Source: Deutsche Bank, Company information
RCC = renal cell carcinoma; ALL = acute lymphoblastic leukaemia; AML = acute myeloid leukaemia; CTCL = cutaneous T-cell lymphoma; CML = chronic myeloid leukaemia; GIST = gastrostromal intestinal tumours

Anaemia (Erythropoietins)

- World market in 2004 valued at more than $10bn
- Two key sub-sectors: renal dysfunction and cancer anaemia
- Growth has slowed from mid/high teens to upper single digits
- Major players are Amgen, J&J, and Roche/Chugai

Physiology

Anaemia is a deficiency of red blood cells, which can lead to a lack of oxygen-carrying ability, causing fatigue and other symptoms such as shortness of breath, heart palpitations, excessive thirst, weight loss, and jaundice. The deficiency occurs either through the reduced production or an increased loss of red blood cells. These cells are manufactured in the bone marrow and have a life expectancy of approximately four months. To produce red blood cells, the body needs (among other things) iron, vitamin B12 and folic acid. If there is a lack of one or more of these nutrients, anaemia will develop. Most cases of iron deficiency in children are caused by eating a poor diet containing little iron. In adults, however, it is most commonly caused by losing blood faster than the body can replace it. Unsurprisingly, anaemia is more common in women due to blood loss in the menstrual cycle and due to the increased iron demands during pregnancy.

Chronic anaemia may result from malfunction of the kidneys or damage to the bone marrow. Specifically, the kidneys secrete a hormone called erythropoietin or EPO, which in turn stimulates the bone marrow to manufacture red blood cells. Hence, patients with impaired or failing kidneys, such as those undergoing renal dialysis, and those receiving bone marrow-depleting chemotherapy, typically experience severe anaemia. The majority of patients requiring chronic anaemia treatment are those with damaged or failing kidneys. In the US, for example, approximately 200,000 people undergo dialysis and are potential candidates for therapy.

Pharmacological treatment

Mild or episodic anaemia arising from iron deficiency can be simply treated by dietary changes, including iron supplementation, while emergency cases may be treated by blood transfusion. However for treatment of chronic disease, including that arising from kidney malfunction or from the side effects of cancer treatment, the main option is to administer injections of biosynthetically-manufactured EPO.

The global market for EPO-based drugs has grown rapidly over the past decade, such that EPO is now the world's biggest selling biopharmaceutical. We estimate that sales in the US, Europe and Japan reached $10.8bn in 2004, up 9% from 2003 (see Figure 283), with two-thirds of sales being recorded in the US. However, growth at 9% represents a slowdown from 2002/3 when the class grew at twice that rate and reflects in part concerns about EPO's efficacy and safety in the oncology setting (which resulted in an FDA Advisory Committee meeting being called in 2004).

Figure 283: The global EPO market, 2002-04 ($m)

$m	Company		2002	2003	2004	Market share
US						
Procrit	J&J	Cancer	3,040	2,804	2,461	37%
Epogen	Amgen	Dialysis	2,260	2,435	2,601	39%
Aranesp	Amgen	Cancer/Dialysis	285	980	1,533	23%
Total US			**5,585**	**6,219**	**6,595**	**100%**
Europe						
Eprex	J&J	Cancer/Dialysis	1,235	1,180	1,128	36%
Neorecormon	Roche	Cancer/Dialysis	616	924	1,040	33%
Aranesp	Amgen	Cancer/Dialysis	132	564	940	30%
Total Europe			**1,982**	**2,668**	**3,108**	**100%**
Japan						
Epogin	Chugai/Roche	Dialysis	488	596	640	66%
Espo	Sankyo	Dialysis	244	270	336	34%
Total Japan			**732**	**866**	**976**	**100%**
Global EPO sales ($m)			**8,299**	**9,753**	**10,679**	
Totals by Product						**(Global share)**
Eprex/Procrit	J&J		4,275	3,984	3589	34%
Epogen	Amgen		2,260	2,435	2601	24%
Aranesp	Amgen		417	1,544	2473	23%
Neorecormon/Epogin	Roche/Chugai		1,104	1,520	1680	16%
Espo	Sankyo		244	270	336	3%

Source: Deutsche Bank estimates and company data

The main manufacturers of EPO are Amgen, Johnson & Johnson, Roche and the latter's affiliate Chugai. The intellectual property position in this market is very complex and explains the differing market positions of the major players. In the main market, namely the US, Amgen holds the patent rights (licensed from its Kirin-Amgen joint-venture with Kirin Brewery) and sells Epogen (erythropoetin alpha) for the indication of anaemia in dialysis patients. J&J also markets EPO in the US under a sub-licence from Amgen, using the brand name Procrit. Procrit is in fact the leading EPO by sales in the US with a 45% share of the market. This drug is identical in all respects to Epogen and carries exactly the same label. Under agreement with Amgen, Procrit is sold for all indications other than anaemia in dialysis patients (although it is allowed to market for pre-dialysis patients). If any sales of Epogen or Procrit slip over into their non-agreed indication, then Amgen must reimburse J&J and vice versa. As part of the agreement, Amgen manufactures Procrit for J&J for the US but not for Europe where J&J sells the drug as Eprex (manufactured at J&J's Puerto Rico plant).

Since 2001, Amgen has also marketed its longer-acting modified EPO, Aranesp (darbepoietin alpha), in the US and Europe for anaemia resulting from cancer chemotherapy and in dialysis patients. Aranesp differs from 'plain' EPO in having two of the 165 amino acids substituted and in its degree of glycosylation (it has five carbohydrate chains attached versus EPO's three, hence its higher molecular weight). Aranesp is priced at a small premium to the other EPOs and only has to be injected once a week, whereas the other EPOs are injected three times a week.

In Europe, J&J's Eprex is the market leader although serious side effect concerns (resulting from a manufacturing issue in 2003) have seen it lose significant share to Roche's NeoRecormon. The latter entered Roche's portfolio in 1997 through its acquisition of Boehringer Mannheim. Originally licensed from Genetics Institute (a unit of Wyeth), NeoRecormon was the subject of a legal settlement in July 2001 between Roche, Amgen and J&J that allowed Roche to continue marketing the drug in Europe. NeoRecormon is sold in Europe for the full range of indications in dialysis and cancer chemotherapy and is priced in line with J&J's Eprex.

In Japan, Roche's 50.1% owned subsidiary Chugai markets EPO under the brand name Epogin. As with Roche and NeoRecormon, Chugai licensed this product from Genetics Institute. Epogin has around a 67% share of the Japanese EPO market, its only competitor being Sankyo's Espo (which is sold under licence from Kirin-Amgen). Sales of EPO in Japan are almost entirely confined to the dialysis setting as the drug has not yet been approved for use in cancer patients.

Figure 284 compares the indications and dosing regimens for the main EPO products in the US and Europe.

Figure 284: Comparison of the marketed EPO-based drugs in US and Europe

Name	Procrit/Epogen	Aranesp	NeoRecormon
Biological molecule	Recombinant Erythropoetin alpha	Recombinant Eryrthropoetin (adjusted)	Recombinant Erythropoetin beta
Weight	30,400 KDa	37,000 KDa	30,400KDa
Company	J&J (Procrit/Eprex), Amgen (Epogen)	Amgen	Roche
Indications			
Dialysis	yes (in US, Epogen only promoted)	yes	yes
Non-Dialysis	yes	yes	yes
Zidovudine-treated HIV patients	yes		
Cancer - Chemo induced	yes	yes	yes
Surgery	yes		yes
Prevention of anaemia in premature infants			yes
Dosing Schedule			
Chronic Renal Failure (dialysis)	Subcutaneous or IV injection	Subcutaneous or IV injection	Subcutaneous or IV injection
Starting dose	50-100 units/kg; 3x/week	0.45mcg/kg; 1x/week	3x20 iu/kg week for SC in divided or single dose; 40 iu/kg week IV
Maintenance	75 units/kg; 3x/week (average in trials)	0.41-0.53mck/kg; 1x/week (average in trials)	Halve the dose then adjust. Patients stable on once weekly SC can be switched to 1x/2weeks
	In trials 95% patients responded and virtually all were transfusion free within two months.	In comparative trial versus Epogen: Study N1 - 72% of Aranesp and 84% of EPO patients achieved Hb target Study N2 - 93% of Aranesp and 92% of EPO patients achieved Hb target	
Zidovudine treated HIV patients	Subcutaneous or IV injection		
Starting dose	50-100 units/kg; 3x/week for 8 weeks		
Maintenance	Adjust up to 300 units/kg		
Cancer - Chemo induced	Subcutaneous or IV injection	Subcutaneous injection	Subcutaneous injection
Starting dose	150 units/kg; 3x/week for 8 weeks	2.25mcg/kg; 1x/week	3 to 7 doses per week
Maintenance	Adjust up to 300 units/kg	In trials dose escalated to 4.5mcg/kg	Can be given weekly SC at 450 iu/kg
Region	US and EU	US and EU	EU only

Source: Deutsche Bank estimates and company data

Clinical endpoints

The primary endpoint of clinical trials for anaemia agents is stimulation of red blood cell production measured as increased blood haemoglobin (Hb) levels.

Pipeline products

Two EPO derivatives are nearing launch. The first is a gene-activated EPO, known as Dynepo, from Transkaryotic Therapies (TKT, soon to be acquired by Shire). This product – which comprises 'plain' EPO manufactured by a different means from the usual fermentation process – has been successfully blocked in the US by litigation from Amgen but may potentially be launched in some European markets. TKT targets a launch in 2006 and signed a supply deal with Lonza in August 2004.

The second product, Roche's R744 or CERA (Continuous Erythropoietin Receptor Activator), is considerably more interesting as it is an improved, long-acting EPO. CERA is a modified erythropoietin analogue that is also pegylated (i.e. attached to PEG polymer chains). Pegylation is used to protect protein-based drugs from the body's immune response and from other clearance mechanisms. This typically leads to greater stability, lower immunogenicity, higher bioavailability and a longer half-life compared with the original drug. Roche speculates that CERA may have a number of key advantages over existing products, including potent, prolonged stimulation of red blood cell production; less frequent dosing (it targets administration once every 3 or 4 weeks); predictable dose-dependent responses; comparable efficacy between subcutaneous and intravenous injections; improved tolerability; and stability at room temperature (other EPOs must be refrigerated). Phase II data in dialysis patients was encouraging and demonstrated that CERA was associated with a potent and sustained increase in red blood cell count, with increasing doses providing a more rapid response. No drug-related severe adverse events were noted and there was no evidence of anti-EPO antibody development. Phase III studies are now ongoing and Roche plans to file for approval in 2006. This would imply US and European launches in 2007, although this would also be subject to Amgen not securing an injunction as part of what we expect to be inevitable patent litigation between Amgen and Roche.

It should also be noted that Amgen's and Roche's European patents on EPO expire over the next few years. However, we doubt that generics will be launched before 2007 or so given the lack of an established approval process for "generic biologics". Indeed, even when generics do eventually arrive in this market, we would expect some reticence by physicians to prescribe these given concerns that differing manufacturing processes may result in EPOs with different levels of activity and, most importantly – given J&J's problems in 2003 – that generic EPOs could carry additional safety risks.

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Europe United Kingdom
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2 August 2005

AstraZeneca

Reuters: **AZN.N** Bloomberg: **AZN UN** Exchange: **NYSE** Ticker: **AZN.N**

Bridging the gap

In April 1999, Astra AB and Zeneca PLC merged to create AstraZeneca. Established as a world-leading life science company, the subsequent agrochemical demerger has left the group wholly focused on healthcare. Following the advent of generic competition to Prilosec in December 2002, AstraZeneca set an aspiration EBIT margin target of 27% with the oncology franchise, Seroquel and Crestor expected to replace lost Prilosec revenues. Setbacks in R&D during 2004 have, however, exacerbated the perception of a 'gap' in AstraZeneca's pipeline.

Growth products drive margin expansion

The arrival of generic competition to Prilosec/Losec in late 2002 and one-off inventory provisions in 2004 have created a significant gross margin headwind, resulting in a 400bp decline in AstraZeneca's operating margin to 21%. Driven by >20% expansion in the growth portfolio over the next four years, which includes Crestor (cholesterol), Symbicort (asthma) and the high margin oncology and Seroquel (schizophrenia) franchises, AstraZeneca has set a 2007 EBIT margin target of 27%. Supported by ongoing productivity initiatives, the achievement of this target would result in premium 20%-plus EPS growth ahead of the maturation of the Phase II pipeline.

Limited pipeline expectations suggest data driven upside

With Exanta (stroke prevention) having failed to gain approval in 2004, no new product launches are expected until 2007 and the pipeline represents less than 5% of consensus valuations. However, AstraZeneca has five key near term pipeline opportunities which could offer combined sales potential upwards of $10bn. These include: Cerovive for stroke, Nexium follow-on AZD0865 for ulcers, anti-clotting agent AZD6140 which will compete with Sanofi's $4.5bn drug Plavix, ZD6474 for lung cancer and Exanta follow-on AZD0837. The successful development of these assets offers significant upside against low expectations.

Patent risk remains manageable against potential generic challenges

Aside from Toprol XL which is set to face generics in 2007, AstraZeneca is not expected to face a major US patent expiry until the loss of Arimidex in 2009. In addition, while generic challenges to key drivers Nexium and Seroquel appear likely, we believe both products are protected by strong compound patents and line-extension/replacement strategies.

Forecasts and ratios

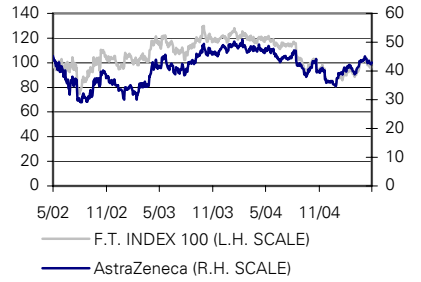
Year End Dec 31	2003A	2004A	2005E	2006E	2007E
Revenue (USD m)	18,849	21,426	23,830	26,184	27,731
EBITA (USD m)	4,046	4,585	6,468	7,546	8,033
Stated PBT (USD m)	4,065	4,892	6,548	7,666	8,203
Stated EPS (USD)	1.76	2.18	2.88	3.52	3.92
P/E (DB EPS) (x)	22.7	22.1	14.5	11.9	10.7
EV/EBITA (x)	16.2	15.5	9.6	8.0	7.2
DPS (USD)	0.79	0.94	1.33	1.63	1.81
Yield (%)	2.0	2.1	3.2	3.9	4.3

Source: Deutsche Bank

Buy

Price at 2 August 2005 (USD)	**45.65**
Price Target (USD)	**50.00**
52-week range (USD)	**48.75-34.72**

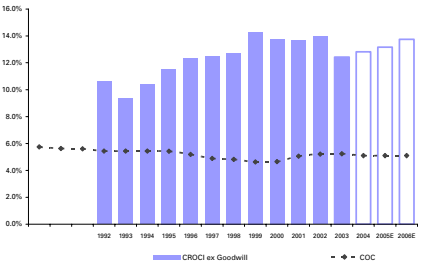
Price/price relative



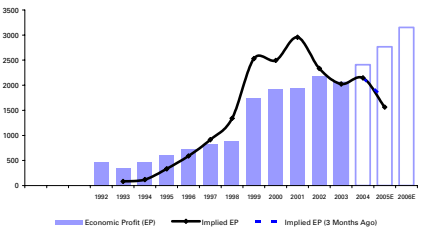
Stock data

Market cap (USD bn)	**67.8**
Shares outstanding (m)	**1,616**
Free float (%)	**100**

Returns ex-Goodwill vs Cost of Capital



Economic/Discounted Economic Profit



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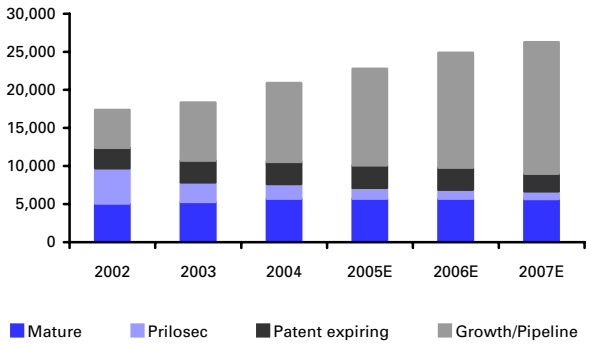
Figure 285: Key expiries and launches 2004-07E

Patent expiries	2004 US Sales	% Pharma	Expiry date
Plendil	$166m	1%	2004
Zoladex	$152m	1%	2005
Pulmicort	$576m	3%	2007
Toprol	$977m	5%	2007

New product	Peak sales	Indication	Launch date
Symbicort (US)	$1,000m	Asthma	2007

Source: Deutsche Bank and Company information

Figure 286: Portfolio shift 2002-07E



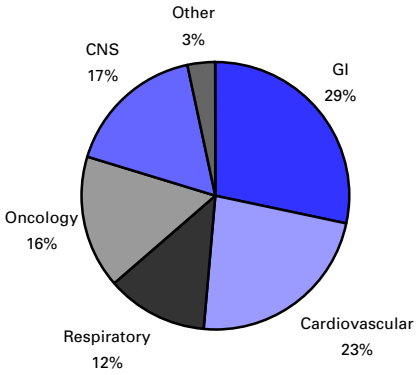
Source: Deutsche Bank and Company information

Figure 287: Summary P&L ($m)

	2002	2003	2004E	2005E	2006E	2007E	CAGR
Sales	17,841	18,849	21,426	23,830	26,184	27,731	9.2%
COGS	(2,995)	(3,254)	(4,049)	(3,863)	(3,900)	(4,010)	6.0%
SG&A	(5,998)	(7,393)	(8,268)	(8,570)	(9,310)	(9,858)	10.4%
R&D	(3,069)	(3,012)	(3,467)	(3,613)	(3,933)	(4,154)	6.2%
EBIT	4,356	4,007	4,547	6,428	7,505	7,990	12.9%
EBITDA	5,316	5,300	5,815	7,747	8,876	9,417	12.1%
EPS ($)	1.84	1.76	2.01	2.88	3.52	3.92	16.4%
COGS %	*16.8%*	*17.3%*	*18.9%*	*16.2%*	*14.9%*	*14.5%*	*-2.9%*
SG&A %	*33.6%*	*39.2%*	*38.6%*	*36.0%*	*35.6%*	*35.6%*	*1.1%*
R&D %	*17.2%*	*16.0%*	*16.2%*	*15.2%*	*15.0%*	*15.0%*	*-2.7%*
EBIT %	*24.4%*	*21.3%*	*21.2%*	*27.0%*	*28.7%*	*28.8%*	*3.4%*

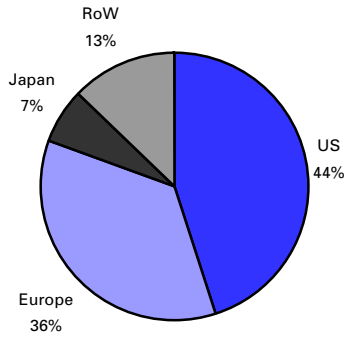
Source: Deutsche Bank and Company information

Figure 288: Sales by therapeutic category 2004



Source: Company information

Figure 289: Sales by geography 2004



Source: Company information

Figure 290: Key pharmaceutical products (sales in $m)

Brand	Generic	Lead Indication	US Expiry	US Exclusivity	Sales 2004	Sales 2008E
Gastrointestinal						
Losec/Prilosec	omeprazole	Ulcers/GERD	Expired	Expired	1947	1069
Nexium	esomeprazole	Ulcers/GERD	Aug-15	Expired	3883	5631
Cardiovascular						
Zestril	lisinopril	Hypertension	Expired	Expired	440	260
Seloken/Toprol	metoprolol	CHF	Mar-08	Expired	1387	298
Plendil	felodipine	Hypertension	Expired	Expired	455	83
Atacand	candesartan	Hypertension	Apr-11	Expired	879	1198
Crestor	rosuvastatin	Cholesterol	Jun-12	Aug-08	908	3114
Respiratory						
Pulmicort	budesonide	Asthma	Sep-07	Expired	1050	1162
Accolate	zafirleukast	Asthma	Sep-10	Expired	116	57
Rhinocort	budesonide	Rhinitis	Oct-17	Expired	361	435
Oxis	formoterol	Asthma	Non-US	Non-US	101	60
Symbicort	formoterol/budesonide	Asthma	Non-US	Non-US	797	1514
Oncology						
Zoladex	goserelin	Prostate Cancer	Aug-05	Expired	917	936
Nolvadex	tamoxifen	Breast Cancer	Expired	Expired	134	70
Casodex	bicalutamide	Prostate Cancer	Oct-08	Expired	1012	1250
Arimidex	anastrozole	Breast Cancer	Dec-09	Expired	811	2343
Faslodex	fluvestrant	Breast Cancer	Oct-04	Apr-07	99	190
CNS						
Zomig	zolmitriptan	Migraine	Nov-12	Expired	356	304
Seroquel	quetiapine	Schizophrenia	Sep-11	Expired	2027	4466
Specialist/Hospital						
Diprivan	propofol	Anaesthetic	Expired	Expired	500	364
Xylocaine	xylocaine	Pain Relief	Expired	Expired	201	244
Merrem	meropenem	Antibiotic	n.a.	n.a.	423	669
Cerovive	n.a.	Stroke	n.a.	n.a.	0	145

Source: Company data, Deutsche Bank estimates

NOTES

Europe United Kingdom
Pharmaceuticals Pharmaceuticals

2 August 2005

GlaxoSmithKline

Reuters: **GSK.L** Bloomberg: **GSK LN** Exchange: **LSE** Ticker: **GSK.L**

Delivering the pipeline

Established from the merger of Glaxo Wellcome and SmithKline Beecham in 2000, GSK is the world's second largest research-based pharmaceutical company with a 7% share of the global market. The company has leading franchises in respiratory products, anti-infectives, CNS disorders and vaccines. The arrival of generic competition to several leading products has undermined recent growth, and a further wave of patent expiries in the medium term suggests that much depends on delivery of the pipeline.

Well-positioned with massive size and scale

GSK has a number of key investment attractions, not least its market leading positions in several important therapeutic categories and a well-respected management team. In addition, its massive sales infrastructure (40,000 representatives globally, including 8,000 in the US), huge R&D budget and strong managed care relationships have made it a partner of choice for licensors.

Medium term patent expiries undermine performance

After a challenging two year period where GSK faced US patent expiries on two of its leading antidepressants, Paxil and Wellbutrin SR, we believe GSK is set to enjoy several years of respectable growth. However, the respite is only temporary as the company faces another wave of patent expiries between 2007 and 2009, which will affect some 10% of the company's sales.

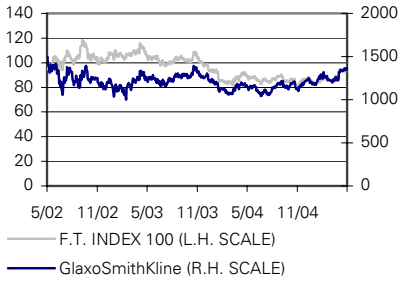
Large and interesting pipeline but still early stage

GSK's pipeline is vast with over 80 new chemical entities (NCEs), 32 product line extensions (PLEs) and 20 vaccines in development. However, the majority of the NCEs (over 85%) are still in Phase I or Phase II development where odds of success are less than 20%. With further patent expiries only 2-4 years away, GSK's ability to sustain longer term growth is heavily dependent on the company's ability to deliver on the pipeline. Thus the key focus for investors in the near term will be on pipeline newsflow including updates on a number of key products such as 497115, an oral small molecule designed to boost platelet levels; lapatinib, a dual kinase inhibitor for breast cancer; and Cervarix a vaccine designed to protect against the human papillomavirus (HPV) which is associated with the majority of cervical cancers.

Hold

Price at 2 August 2005 (GBP)	**1,336.00**
Price Target (GBP)	**1,330.00**
52-week range (GBP)	**1,367.00-1,042.00**

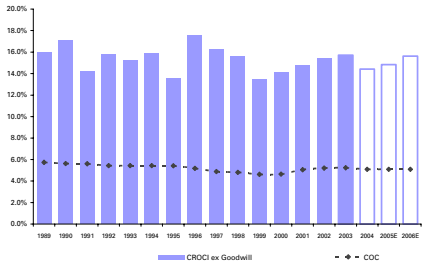
Price/price relative



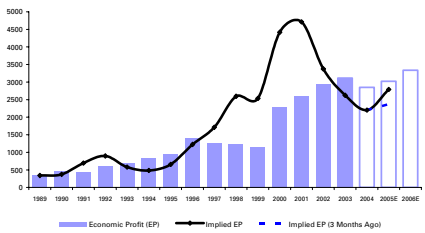
Stock data

Market cap (GBP bn)	**77.7**
Shares outstanding (m)	**5,656**
Free float (%)	**100**

Returns ex-Goodwill vs Cost of Capital



Economic/Discounted Economic Profit



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Forecasts and ratios

Year End Dec 31	2003A	2004A	2005E	2006E	2007E
Revenue (GBP m)	21,070	19,986	21,591	23,156	23,779
EBITA (GBP m)	6,532	5,848	6,684	7,273	7,499
Stated PBT (GBP m)	6,349	5,779	6,568	7,180	7,432
Stated EPS (GBp)	72.36	68.13	81.09	90.00	94.48
P/E (DB EPS) (x)	15.6	16.4	17.0	15.3	14.6
EV/EBITA (x)	11.0	11.5	11.8	10.8	10.4
DPS (GBp)	41.00	42.00	43.00	44.00	45.00
Yield (%)	3.3	3.7	3.1	3.2	3.3

Source: Deutsche Bank

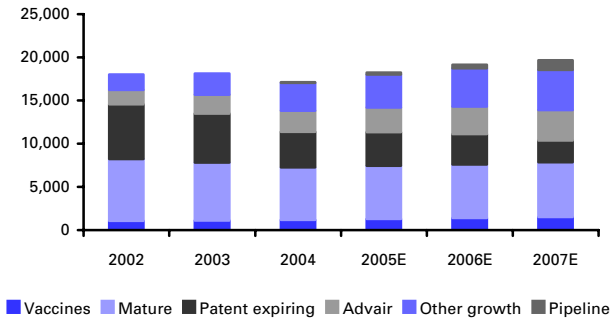
Figure 291: Key expiries and launches 2004-07E

Patent expiries	2004 US Sales	% Pharma	Expiry date
Wellbutrin	£410m	2%	2004
Flonase	£450m	3%	2005**
Zofran	£565m	3%	2007
Coreg	£425m	2%	2007
Imitrex	£492m	3%	2007*
New product	**Peak sales**	**Indication**	**Launch date**
Vesicare	$400m	Incontinence	2005
Boniva	$500m	Osteoporosis	2005
nelarabine	$200m	Leukaemia	2005
Rotarix	$500m	Rotavirus (vaccine)	2006
640385	$200m	HIV	2007
Avamys ('698)	$500m	Allergy	2007
597599	$300m	Emesis	2007
Cervarix	>$1,000m	HPV (vaccine)	2007

**Assumes litigation successful **Pending issue of FDA guidance*

Source: Deutsche Bank and Company information

Figure 292: Portfolio shift 2002-07E (£m)



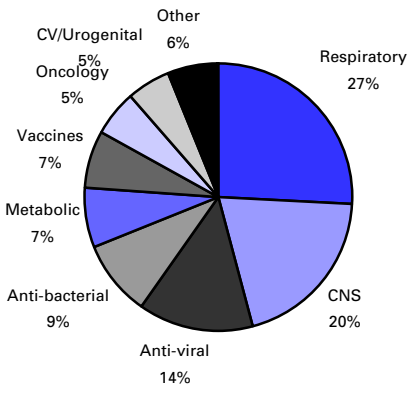
Source: Deutsche Bank and Company information

Figure 293: Summary P&L (£m)

	2002	2003	2004E	2005E	2006E	2007E	CAGR
Sales	21,212	21,070	19,986	21,591	23,156	23,779	2.3%
Of which pharma	17,995	18,114	17,100	18,625	20,086	20,563	2.7%
COGS	(4,243)	(4,221)	(4,360)	(4,691)	(4,875)	(4,969)	3.2%
SG&A	(7,543)	(7,434)	(6,905)	(7,153)	(7,645)	(7,751)	0.5%
R&D	(2,732)	(2,844)	(2,904)	(3,101)	(3,313)	(3,510)	5.1%
EBIT	6,583	6,445	5,756	6,684	7,273	7,499	2.6%
EBITDA	7,492	7,511	6,686	7,609	8,237	8,502	2.6%
EPS (p)	78.3	77.2	68.1	81.1	90.0	94.5	3.8%
COGS %	*20.0%*	*20.0%*	*21.8%*	*21.7%*	*21.1%*	*20.9%*	*0.9%*
SG&A %	*35.6%*	*35.3%*	*34.5%*	*33.1%*	*33.0%*	*32.6%*	*-1.7%*
R&D %	*12.9%*	*13.5%*	*14.5%*	*14.4%*	*14.3%*	*14.8%*	*2.8%*
EBIT %	*31.0%*	*30.6%*	*28.8%*	*31.0%*	*31.4%*	*31.5%*	*0.3%*

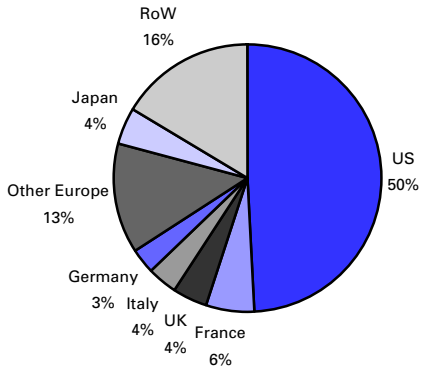
Source: Deutsche Bank and Company information

Figure 294: Sales by therapeutic category 2004



Source: Company information

Figure 295: Sales by geography 2004



Source: Company information

Figure 296: Key pharmaceutical products (sales in £m)

Brand	Generic	Lead Indication	US patent	US exclusivity	Sales 2004	Sales 2008E
GI/Metabolism						
Zantac	ranitidine	Ulcers	Expired	Expired	273	211
Avandia	rosiglitazone	Diabetes	2011*	Expired	1114	2083
Respiratory						
Ventolin	albuterol	Asthma	Expired	Expired	239	210
Serevent	salmeterol	Asthma	Feb-08	Expired	349	160
Flixotide/Flovent	fluticasone	Asthma	Expired	Expired	618	570
Flixonase/Flonase	fluticasone	Rhinitis	Expired	Expired**	578	163
Seretide/Advair	salmeterol/fluticasone	Asthma	Sep-10	Expired	2441	3774
Antiviral						
Zovirax	aciclovir	Herpes	Expired	Expired	147	101
Valtrex	valaciclovir	Herpes	Jun-09	Expired	571	977
Epivir	lamivudine	HIV	May-10	Expired	294	254
Combivir	zidovudine/lamivudine	HIV	May-10	n.a.	570	558
Ziagen	abacavir	HIV	Jun-12	Expired	155	120
Trizivir	zidovudine/lamivudine/abacavir	HIV	Jun-12	n.a.	322	256
Lexiva	fosamprenavir	HIV	Dec-17	Oct-06	59	158
Zeffix	lamivudine	Hepatitis B	May-10	Expired	130	147
Antibacterial						
Zinnat/Ceftin	cefuroxime	Antibiotic	Expired	Expired	205	185
Fortum/Fortaz	ceftazidime	Antibiotic	Expired	Expired	155	133
Augmentin (incl XR, ES)	amoxicillin/clavulanate	Antibiotic	Expired	Expired	708	585
Oncology						
Zofran	ondansetron	Emesis	Dec-06	Expired	763	214
n.a.	nelarabine	Leukaemia	n.a.	n.a.	0	200
Hycamtin	topotecan	Ovarian cancer	Jan-10	Expired	99	120
Central Nervous System						
Imigran/Imitrex	sumatriptan	Migraine	Jun-07	Expired	682	165
Lamictal	lamotrigine	Epilepsy	Jan-09	Aug-05	677	914
Wellbutrin (incl SR, XL)	bupropion	Depression	Oct-18 (XL)	Expired	751	331
Paxil (incl CR)	paroxetine	Depression	Dec-12 (CR)	Expired	1063	632
Cardiovascular						
Coreg/Kredex	carvedilol	CHF/Hypertension	Mar-07	Expired	432	430
Other						
Boniva (WW co-promo)	ibandronate	Osteoporosis	2012	May-08	0	115***
Vesicare (US co-promo)	solifenacin	Urinary incontinence	Dec-15	Nov-09	0	159
Avodart	dutasteride	BPH	2015*	Nov-06	64	354
Vaccines	n.a.	Various	n.a.	n.a.	1121	2379

*Source: Company data, Deutsche Bank estimates *Assumes patent term extension. **Generics delayed pending FDA guidance on approval procedure for intranasal drugs. ***Consolidated sales*

NOTES

Europe Germany
Pharmaceuticals Pharmaceuticals

2 August 2005

Merck KGaA

Reuters: **MRCG.DE** Bloomberg: **MRK GY** Exchange: **GER** Ticker: **MRCG.DE**

Liquid crystals and Erbitux drive growth

Founded in 1668 Merck is pharmaceutical chemical conglomerate with six different business units and revenues of Euro 5.3bn in 2004. Merck has streamlined the business with several divestments in the last few years and strengthened its focus on key drivers, liquid crystals and oncology. Seventy-six percent of the shares are held by the family (E. Merck OHG), while roughly 50m shares are freefloat.

Strong growth due to product mix

We forecast for Merck's continued business 10% sales and operating profit growth p.a. until 2008E. Although our margin expansion forecast (increasing from 14.3% in 2004 to 20.5% in 2008E) sounds spectacular, our model only foresees stable divisional margins and higher earnings from its new cancer drug Erbitux. We did not assume any major new product launches in our model. Merck has three cancer compounds in Phase II and a Parkinson drug in Phase III.

Liquid crystals the key driver

We expect Merck's LCD business (40% of 2004 operating profit) to grow 25% while keeping its 50% operating margin until 2008E. Due to strong intellectual property, Merck has a monopoly as the liquid crystal supplier for flat-screen TVs. Scale effects and mix improvement within different LCD applications should keep profitability at exceptionally high levels. The greatest risk to our forecast would be a superior new technology (e.g. organic light-emitting diodes or OLEDs), which are several years out before large scale applications might become affordable.

Pharma margin expansion due to Erbitux

Merck's ethical business (18% of group profits in 2004) runs at a pedestrian 9% operating margin, as Merck spends 25% of its sales for R&D. With the launch of the high-margin cancer compound Erbitux in 2004 ethical profitability should reach the mid-teens by 2008E. Lacking major high margin drugs in its existing portfolio the generic risk for Merck is relatively low. The respiratory drug Duoneb (4% of pharma sales) is the only compound at risk. We expect Merck's generic and OTC business to keep its margin in the lower mid-teens.

Forecasts and ratios

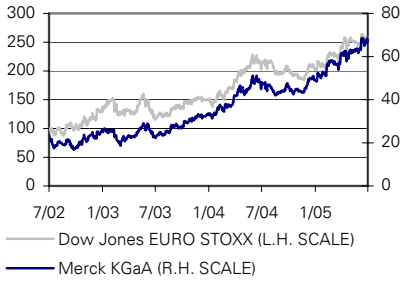
Year End Dec 31	2003A	2004A	2005E	2006E	2007E
Revenue (EUR m)	7,202	5,859	5,824	6,376	7,031
EBITA (EUR m)	2,716	1,314	881	1,076	1,301
Stated PBT (EUR m)	2,543	1,172	822	1,018	1,238
Stated EPS (EUR)	12.89	4.58	2.93	3.66	4.46
DB EPS growth (%)	547.0	-62.2	-45.6	25.0	22.0
P/E (DB EPS) (x)	1.8	8.0	23.1	18.5	15.2
EV/EBITA (x)	2.6	6.8	14.8	11.8	9.5
DPS (EUR)	0.80	0.80	0.80	0.80	0.80
Yield (%)	3.1	1.9	1.2	1.2	1.2

Source: Deutsche Bank

Buy

Price at 2 Aug 2005 (EUR)	**74.00**
Price Target (EUR)	**75.00**
52-week range (EUR)	**68.56-42.06**

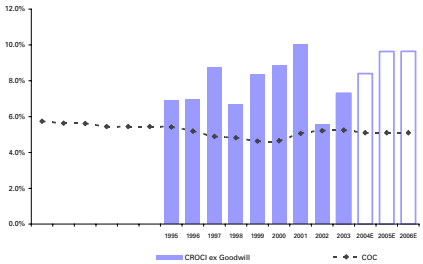
Price/price relative



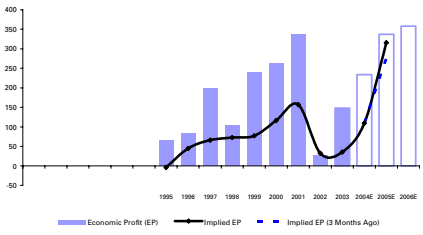
Stock data

Market cap (EUR bn)	**12.6**
Shares outstanding (m)	**190**
Free float (%)	**24**

Returns ex-Goodwill vs Cost of Capital



Economic/Discounted Economic Profit



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Figure 297: Key expiries and launches 2004-07E

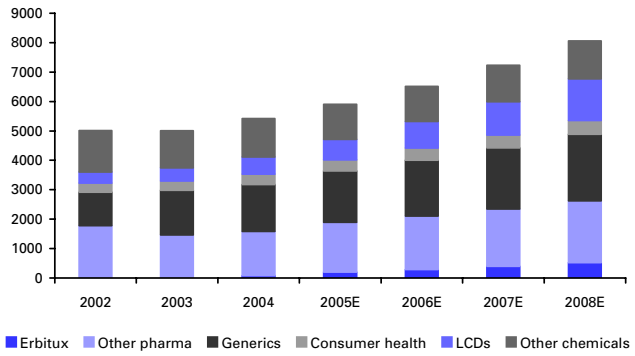
Patent expiries	2004 US Sales	% Pharma	Expiry date
Glucophage XR/ Glucovance*	<Euro 50m	1%	2004
Duoneb	Euro 140m	4%	2005**

New product	Peak sales	Indication	Launch date
Erbitux***	$600m	Cancer	2004
Campral	<$100m	Alcoholism	2004
Advicor***	<$100m	Dyslipidaemia	2005

**Royalties via licensing agreement to BMS*
***If litigation successful.*
****Erbitux rights ex-US; Advicor right ex-North America and Japan*

Source: Deutsche Bank and Company information

Figure 298: Portfolio shift (2002-07E, Euro m)



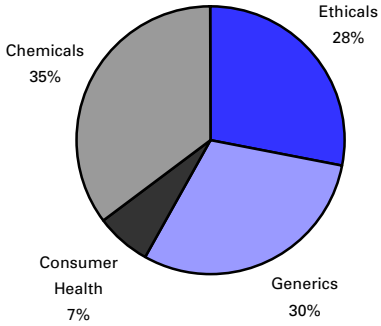
Source: Deutsche Bank and Company information

Figure 299: Merck KGaA Summary P&L (continuing businesses, Euro m)

	2003	2004E	2005E	2006E	2007E	CAGR
Sales	5,003	5,340	5,824	6,376	7,031	8.9%
Of which pharma	3,303	3,452	3,883	4,207	4,570	8.5%
COGS	2,074	2,249	2,402	2,573	2,805	7.8%
SG&A	1,667	1,736	1,816	1,941	2,078	5.7%
R&D	605	599	711	768	832	8.3%
EBIT	657	755	895	1,093	1,316	19.0%
EBITDA	930	1,110	1,256	1,472	1,714	16.5%
EPS, adjusted	2.05	2.67	2.92	3.63	4.43	21.3%
COGS %	*-8.5%*	*-8.9%*	*-8.7%*	*-8.7%*	*-9.2%*	*2.0%*
SG&A %	*-6.9%*	*-6.9%*	*-6.6%*	*-6.6%*	*-6.8%*	*-0.1%*
R&D %	*-2.5%*	*-2.4%*	*-2.6%*	*-2.6%*	*-2.7%*	*2.4%*
EBIT %	*13.1%*	*14.1%*	*15.4%*	*17.1%*	*18.7%*	*9.3%*

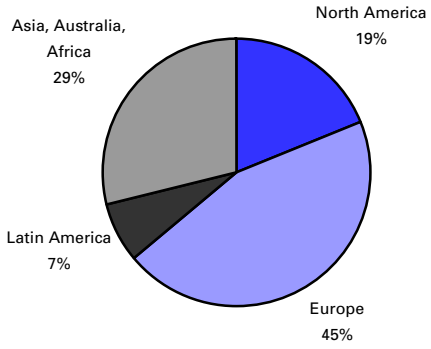
Source: Deutsche Bank, Company information

Figure 300: Sales by category 2004*



*Source: Company information *Continuing businesses*

Figure 301: Sales by geography 2004



Source: Company information

Figure 302: Merck divisional analysis (sales in Euro m)

Division	Key products and markets	Sales 2004	Sales 2008E
Pharmaceuticals			
Ethicals	Erbitux (cancer), Glucophage (diabetes), Concor (hypertension)	1504	2192
Generics	Regional subsidaries include Genpharm, Dey, Generics UK, Alphapharm	1597	2328
Consumer Health	Vitamins/minerals, natural products and cough/colds	352	447
Chemicals			
Liquid crystals	Liquid crystals for use in flat screen televisions, notebooks and mobile phones	583	1532
Pigments	Coatings for automobiles, high tech products and packaging	331	409
Life Science & Analytics	High purity reagents, organic chemicals, culture media and test kitsfor use by pharmaceutical, chemical and food industries	774	874

Source: Company data, Deutsche Bank estimates

NOTES

Europe Switzerland
Pharmaceuticals Pharmaceuticals

2 August 2005

Novartis

Reuters: **NOVN.VX** Bloomberg: **NOVN VX** Exchange: **VTX** Ticker: **NOVN.VX**

Pipeline unlikely to sustain pharma momentum

Novartis was created in 1996, following the merger of the Swiss companies Ciba and Sandoz. The spin-out of its agrochemicals activities left Novartis predominantly focused on human health with ethical pharmaceuticals dominating (65% of sales). Aside from prescription drugs, Novartis also has leading positions in consumer health (18% of sales), ophthalmics (5% of sales) and generics (11% of sales).

Core brands and new products driving growth
From 2000 to 2002, Novartis launched more new drugs than any other global pharmaceutical major. Together with a greater emphasis on the US marketing of core brands such as Diovan and Lotrel, this helped to drive 12% 2000-05E compound growth.

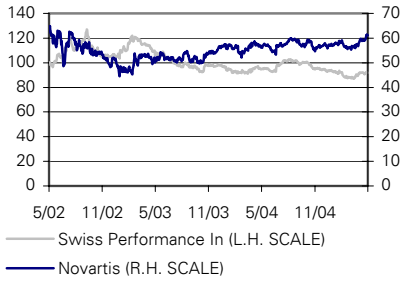
Patent expiries start to bite in 2006/7
While the current product mix is forecast to sustain low-to-mid teens near term earnings growth, Novartis will begin to face a series of patent expiries in 2006 and 2007, which will put pressure on the top and bottom line. Comprising this patent hit are several small products which are collectively worth 7% of sales, as well as Novartis' $1bn hypertension drug Lotrel. While the Lotrel expiry is a matter of contention with the company forecasting protection through 2017 via a combination patent, we expect the drug will face early generics, placing a further 5% of sales at risk.

Growth depends on pipeline
As the current portfolio starts to go ex-growth in 2007, greater emphasis is placed on the successful development of the pipeline. Although Novartis offers a broad and robust pipeline, recent disappointing efficacy data for a few of the key late stage opportunities (e.g. SPP100 for hypertension, PTK787 for cancer) have undermined previously high expectations. Eight other late-stage "focus" R&D projects continue on track, and if successful, could offer significant revenue opportunities. However, we expect investors will demand greater visibility on the pipeline before awarding the shares a premium rating.

Hold

Price at 2 August 2005 (CHF)	**63.00**
Price Target (CHF)	**61.00**
52-week range (CHF)	**61.40-53.25**

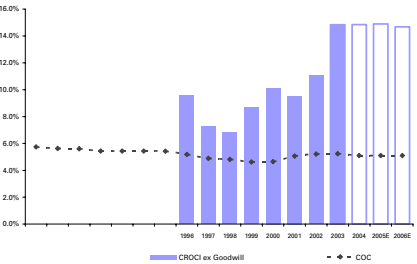
Price/price relative



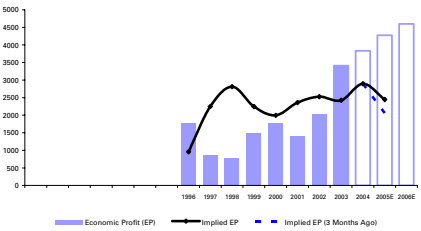
Stock data

Market cap (CHF bn)	**141.3**
Shares outstanding (m)	**2,314**
Free float (%)	**100**

Returns ex-Goodwill vs Cost of Capital



Economic/Discounted Economic Profit



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Forecasts and ratios

Year End Dec 31	2003A	2004A	2005E	2006E	2007E
Revenue (USD m)	24,864	28,247	32,677	36,697	38,814
EBITA (USD m)	5,989	6,289	7,075	8,347	8,968
Stated PBT (USD m)	6,068	6,693	7,407	8,584	9,362
Stated EPS (USD)	2.03	2.37	2.69	3.18	3.54
P/E (DB EPS) (x)	17.9	19.4	17.7	15.0	13.5
EV/EBITA (x)	13.4	14.8	14.8	12.4	11.5
DPS (USD)	0.81	0.89	0.98	1.08	1.18
Yield (%)	2.1	1.9	2.1	2.3	2.5

Source: Deutsche Bank

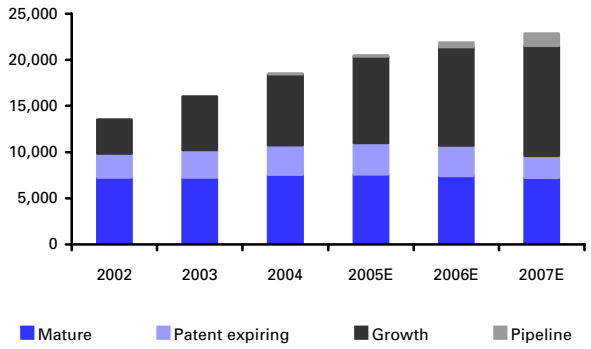
Figure 303: Key expiries and launches 2004-07E

Patent expiries	2004 US Sales	% Pharma	Expiry date
Lotensin	$77m	<1%	2004
Trileptal	$391m	2%	2006
Lamisil	$528m	3%	2007
Tegretol XR	$103m	1%	2007
Lotrel	$920m	5%	2007*
New product	**Peak sales**	**Indication**	**Launch date**
Enablex	$350m	Incontinence	2005
Certican	$300m	Transplant	2005/6
Exjade (ICL670)	$500m	Iron overload	2005/6
LDT600	$150m	Hepatitis B	2006
LAF237	$500m	Diabetes	2007
SPP100	$350m	Hypertension	2007
Lucentis	$500m	AMD	2007

**Assumes litigation unsuccessful*

Source: Deutsche Bank and Company information

Figure 304: Portfolio shift (2002-07E, $m)



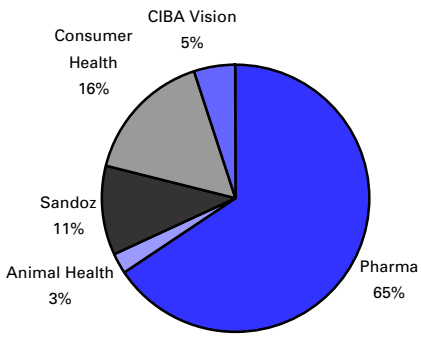
Source: Deutsche Bank and Company information

Figure 305: Summary P&L ($m)

	2002	2003	2004E	2005E	2006E	2007E	CAGR
Sales	20,877	24,864	28,247	32,677	36,697	38,814	13.2%
Of which pharma	13,528	16,020	18,497	20,471	21,820	22,828	11.0%
COGS	(4,994)	(5,894)	(7,268)	(8,991)	(9,902)	(10,864)	16.8%
SG&A	(7,948)	(9,325)	(10,767)	(12,182)	(13,571)	(13,897)	11.8%
R&D	(2,843)	(3,756)	(4,077)	(4,602)	(5,065)	(5,283)	13.2%
EBIT	5,092	5,889	6,289	7,075	8,347	8,968	12.0%
EBITDA	6,038	7,170	7,475	8,426	9,949	10,567	11.8%
EPS ($)	1.84	2.00	2.36	2.68	3.17	3.52	13.9%
COGS %	*23.9%*	*23.7%*	*25.7%*	*27.5%*	*27.0%*	*28.0%*	*3.2%*
SG&A %	*38.1%*	*37.5%*	*38.1%*	*37.3%*	*37.0%*	*35.8%*	*-1.2%*
R&D %	*13.6%*	*15.1%*	*14.4%*	*14.1%*	*13.8%*	*13.6%*	*0.0%*
EBIT %	*24.4%*	*23.7%*	*22.3%*	*21.7%*	*22.7%*	*23.1%*	*-1.1%*

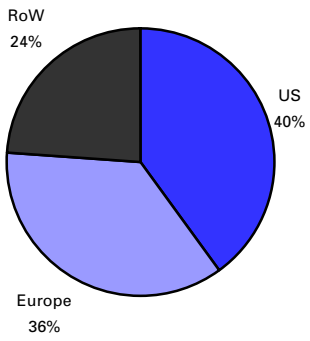
Source: Deutsche Bank and Company information

Figure 306: Sales by division 2004



Source: Company information

Figure 307: Sales by geography 2004



Source: Company information

Figure 308: Key pharmaceutical products (sales in $m)

Brand	Generic	Lead Indication	US patent	US Exclusivity	Sales 2004	Sales 2008E
Cardiovascular						
Lotrel	benazepil/amlodipine	Hypertension	Jan-07	Expired	920	91
Lotensin/Cibacen	benazepril	Hypertension	Expired	Expired	204	20
Diovan	valsartan	Hypertension	Mar-12	Expired	3093	4926
Lescol	fluvastatin	Cholesterol	Oct-11	Expired	758	635
SPP100	aliskiren	Hypertension	n.a.	n.a.	0	350
Bone & Inflammation						
Voltaren	diclofenac	Pain	Expired	Expired	638	708
Miacalcic	calcitonin	Osteoporosis	Mar-15	Expired	377	320
Respiratory						
Foradil	formoterol	Asthma	Mar-19	Feb-06	321	342
Xolair	olizumab	Asthma	Biologic	Biologic	0	250
Central Nervous System						
Clozaril	clozapine	Schizophrenia	Expired	Expired	308	228
Tegretol XR	carbamazepine	Epilepsy	Jul-07	Expired	396	257
Trileptal	oxcarbazepine	Epilepsy	n.a.	Jan-05	518	217
Exelon	rivastigamine	Alzheimer's	2012*	Apr-05	422	530
Transplantation						
Sandimmun/Neoral	cyclosporine	Transplant rejection	Expired	Expired	1011	724
Myfortic	mycophenolic acid	Transplant rejection	n.a.	n.a.	25	150
Certican	everolimus	Transplant rejection	n.a.	n.a.	10	175
FTY720	n.a.	Transplant rejection	n.a.	n.a.	0	60
Oncology						
Sandostatin	octreotide	Cancer	Jul-16 (LAR)	Expired	827	860
Zometa	zoledronate	Bone metasteses	2012*	Aug-06	1078	1519
Gleevec	imatinib	CML	May-13	May-06	1634	2889
Femara	letrozole	Breast cancer	Jun-11	Expired	386	1057
Exjade (ICL670)	n.a.	Iron overload	n.a.	n.a.	0	500
Ophthalmology						
Visudyne	verteporfin	AMD	Aug-15	Expired	448	659
Lucentis	ranibizumab	AMD	n.a.	n.a.	0	350
Other						
Lamisil	terbinafine	Fungal infections	Dec-06	Expired	1162	480
Elidel	pimecrolimus	Eczema	Dec-16	Jun-07	349	509
Famvir	famiciclovir	Cold sores/herpes	Sep-10	Expired	255	301
Enablex	darifenacin	Urinary incontinence	Mar-10	Dec-09	0	150
Zelnorm	tegaserod	IBS	Apr-13	Jul-07	299	886
Starlix	nateglinide	Diabetes	2009*	Dec-05	161	213
LAF237	n.a.	Diabetes	n.a.	n.a.	0	200
Estraderm franchise	estradiol	HRT	n.a.	n.a.	218	203

*Source: Company data, Deutsche Bank estimates *Assumes patent term extension*

NOTES

Europe Denmark
Pharmaceuticals Pharmaceuticals

2 August 2005

Novo-Nordisk

Reuters: **NOVOb.CO** Bloomberg: **NOVO DC** Exchange: **CPH** Ticker: **NOVOb.CO**

Driven by diabetes

Founded in 1923 to manufacture insulin, Novo Nordisk is now the world's leading producer and, using its expertise in recombinant technologies and purification, has developed strong positions in markets for other human proteins. Its increasing focus on biopharmaceuticals has resulted in a low patent expiration profile and the potential for developing high margin, specialist products. Novo has set for itself long term targets which include 15% annual operating profit growth supported by the successful commercialisation of Novoseven in hemophilia and bleeding disorders.

Improvement of product mix key to driving growth

With 65% of revenues from insulin (where Novo has a global volume share of around 51%), growth over and above that in the diabetic population (around 5% p.a.) depends upon improving mix through product development and delivery mechanism innovation. Driven by the launch of premium-priced insulin analogues (Novorapid, Novomix and more recently Levemir) and disposable pen devices, Novo's insulin franchise is currently delivering mid-teens growth. We expect the insulin franchise to deliver similar growth going forward, with insulin analogues still accounting for just 37% of the global insulin market.

New competitors threaten insulin franchise

Novo is set to face competitive threats to its insulin franchise from the roll-out of drugs such as Lilly's Byetta (a so-called GLP-1 analogue) as well as the potential launch of the first inhaled insulin competitor, Exubera, from Pfizer and Nektar. However, given that Byetta's competitive threat will be limited by its dosing schedule (twice daily injections) and Novo has its own GLP-1 analogue (liraglutide) and inhaled insulin (AERx) in development, slated for launch in 2008 and 2009, respectively, downside risk to long term fundamentals seems limited in our view.

Growth from NovoSeven dependent on new indications

Growth in recent years has been augmented by Novo's highly profitable recombinant blood clotting agent, NovoSeven. However, with the market for the product's initial haemophilia indications largely saturated, continued double-digit growth will depend on broadening the product's off-label usage and indications into trauma, intra-cranial hemorrhage (ICH) and other surgical indications. EU approval decisions are expected for trauma and ICH in H2 2005, with further Phase II data in cardiac surgery, spinal surgery, upper GI bleeds and brain injury expected in H1 2006.

Forecasts and ratios

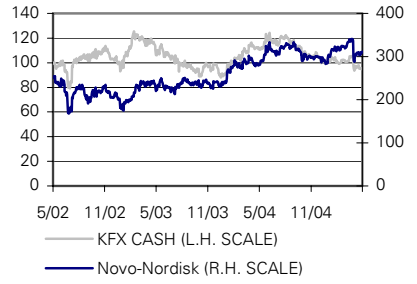
Year End Dec 31	2003A	2004A	2005E	2006E	2007E
Revenue (DKK m)	26,158	29,031	32,626	36,176	39,586
EBITA (DKK m)	6,422	6,980	7,722	8,957	10,136
Stated PBT (DKK m)	7,376	7,457	7,640	8,789	10,031
Stated EPS (DKK)	14.15	14.83	16.48	18.79	21.59
P/E (DB EPS) (x)	16.1	19.8	19.1	16.7	14.6
EV/EBITA (x)	11.9	14.0	13.3	11.3	9.6
DPS (DKK)	4.40	4.80	5.48	6.44	7.61
Yield (%)	1.9	1.6	1.7	2.0	2.4

Source: Deutsche Bank

Hold

Price at 2 August 2005 (DKK)	**317.00**
Price Target (DKK)	**325.00**
52-week range (DKK)	**340.50-281.00**

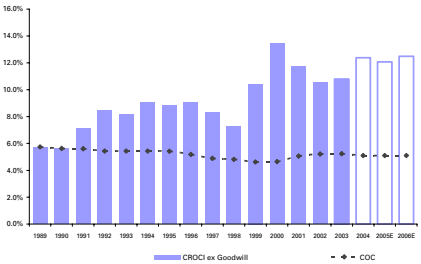
Price/price relative



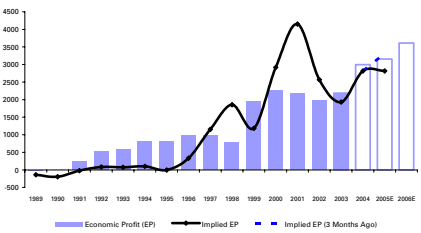
Stock data

Market cap (DKK bn)	**103.5**
Shares outstanding (m)	**329**
Free float (%)	**100**

Returns ex-Goodwill vs Cost of Capital



Economic/Discounted Economic Profit



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Figure 309: Key expiries and launches 2004-07E

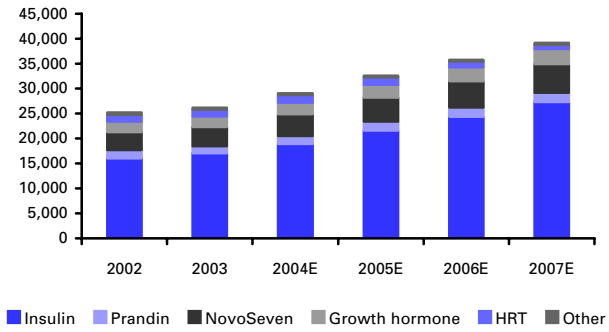
Patent expiries	2004 US Sales	% Pharma	Expiry date
None			

New product	Peak sales	Indication	Launch date
Levemir	DKK 3.6bn	Diabetes (insulin)	2006
NovoSeven	DKK 0.7bn	ICH	2006/8*
NovoSeven	DKK 1.8bn	Trauma	2006/8*

**EU filing. Dependent on whether additional studies required.*

Source: Deutsche Bank and Company information

Figure 310: Porftolio shift (2002-07E, DKK m)



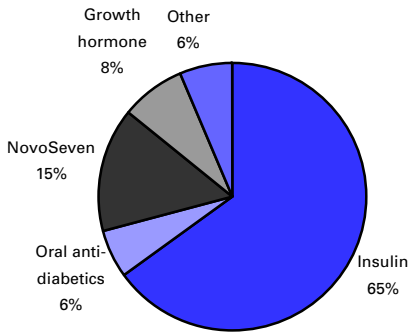
Source: Deutsche Bank and Company information

Figure 311: Summary P&L (DKK m)

	2002	2003	2004E	2005E	2006E	2007E	CAGR
Sales	25,040	26,158	29,031	32,626	36,176	39,586	9.6%
COGS	(6,594)	(7,409)	(8,050)	(8,804)	(9,310)	(9,792)	8.2%
SG&A	(9,294)	(9,308)	(10,224)	(11,475)	(12,610)	(13,957)	8.5%
R&D	(3,945)	(4,055)	(4,352)	(4,959)	(5,643)	(6,057)	9.0%
Royalties & other	758	1,036	575	335	345	355	-14.1%
EBIT	5,965	6,422	6,980	7,722	8,957	10,136	11.2%
EBITDA	7,297	8,003	8,872	9,652	10,926	12,144	10.7%
EPS (DKK)	11.86	14.15	14.83	16.48	18.79	21.59	12.7%
COGS %	*26.3%*	*28.3%*	*27.7%*	*27.0%*	*25.7%*	*24.7%*	*-1.2%*
SG&A %	*37.1%*	*35.6%*	*35.2%*	*35.2%*	*34.9%*	*35.3%*	*-1.0%*
R&D %	*15.8%*	*15.5%*	*15.0%*	*15.2%*	*15.6%*	*15.3%*	*-0.6%*
EBIT %	*23.8%*	*24.6%*	*24.0%*	*23.7%*	*24.8%*	*25.6%*	*1.5%*

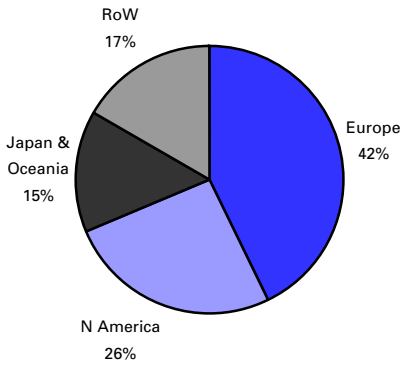
Source: Deutsche Bank and Company information

Figure 312: Pharma sales by category 2004



Source: Company information

Figure 313: Sales by geography 2004



Source: Company information

Figure 314: Key pharmaceutical products (sales in DKK m)

Brand	Generic	Lead Indication	Sales 2004	Sales 2008E
Diabetes				
Insulin	Insulin	Diabetes	18890	30323
Prandin	repaglinide	Diabetes	1643	1965
Hormones				
Norditropin	human growth hormone	Growth hormone deficiency	2317	3238
HRT franchise	oestrogen	HRT	1488	809
Haemophilia				
NovoSeven	Factor VII	Haemophilia	4359	6475

Source: Company data, Deutsche Bank estimates

NOTES

Europe Switzerland
Pharmaceuticals Pharmaceuticals

2 August 2005

Roche Holding AG

Reuters: **ROG.VX** Bloomberg: **ROG VX** Exchange: **VTX** Ticker: **ROG.VX**

Biologicals fueling growth

Roche is one of Europe's leading pharmaceutical companies and remains family controlled. Roche has strong franchises in oncology and infectious diseases, and through its 55% holding in Genentech is well exposed to developing markets for biotech-based products. Roche has also enhanced its access to the Japanese market via its 51% interest in Chugai. Aside from pharmaceuticals, Roche has a market-leading diagnostics division which contributes roughly one-quarter of Group sales.

Biotech and oncology portfolio driving pharma growth

Roche's sales momentum is forecast to show 12% compound growth to 2008E, roughly twice the growth rate of the broader market. This is expected to be driven by an improving sales mix in the pharmaceutical division, led by significant expansion in Avastin (colorectal, lung, breast cancer) and Herceptin (breast cancer) sales, with 'biotech' (i.e. protein- and antibody-based) drugs set to reach 67% of sales by 2008E, compared to 43% in 2003. Importantly, the specialty nature of these products means they do not require massive sales and marketing efforts and thus represent high-margin sales, while the current lack of a regulatory approval pathway for biologics suggests a lower generic risk.

Diagnostics continues to grow ahead of market

Roche's diagnostics division is the world leader in in-vitro diagnostics with 21% global market share in 2004, up from 15% in 2000. The division offers products and services across several key areas of testing including centralised diagnostics (analysis of blood and other body fluids performed in a centralised testing laboratory), molecular diagnostics (screening for pathogens or personalised genomic markers) and diabetes care (blood glucose monitoring products and insulin delivery systems).

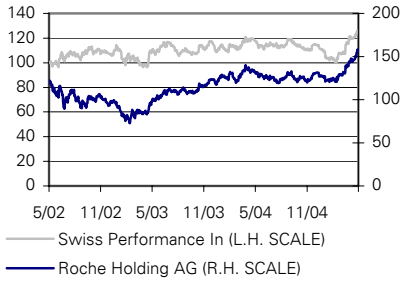
Strategic disposals and acquisitions strengthening focus

Over the past several years, Roche has reduced its dependence on financial income (which as recently as 2000 comprised 20% of pre-tax profits) and has significantly improved transparency. In addition, the company's acquisition of a 51% interest in Chugai and disposal of its vitamins and OTC/consumer health operations have focused its business on its core prescription pharmaceuticals and diagnostics divisions.

Buy

Price at 2 August 2005 (CHF)	**176.50**
Price Target (CHF)	**190.00**
52-week range (CHF)	**157.90-119.25**

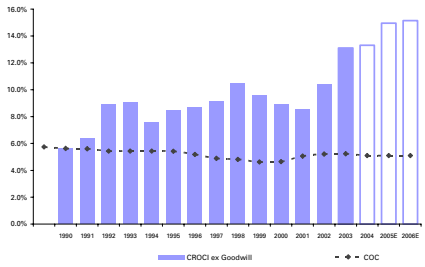
Price/price relative



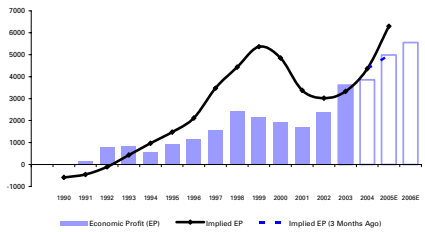
Stock data

Market cap (CHF bn)	**142.0**
Shares outstanding (m)	**841**
Free float (%)	**100**
Shares issued	**Genusscheine 681m**
	Bearer (voting) 160m

Returns ex-Goodwill vs Cost of Capital



Economic/Discounted Economic Profit



Forecasts and ratios

Year End Dec 31	2002A	**2003A**	2004E	2005E	2006E
Revenue (CHF m)	27,190	29,523	34,233	38,265	42,733
EBITA (CHF m)	6,009	6,568	8,439	10,794	13,150
DB PBT (CHF m)	6,321	8,170	9,589	12,106	14,642
DB EPS (CHF)	4.79	6.30	7.41	9.40	11.40
P/E (DB EPS) (x)	21.0	20.1	22.2	17.5	14.4
EV/EBITA (x)	19.2	20.4	18.9	14.3	11.2
DPS (CHF)	1.65	2.00	2.30	2.75	3.30
Yield (%)	1.6	1.6	1.4	1.7	2.0

Source: Deutsche Bank

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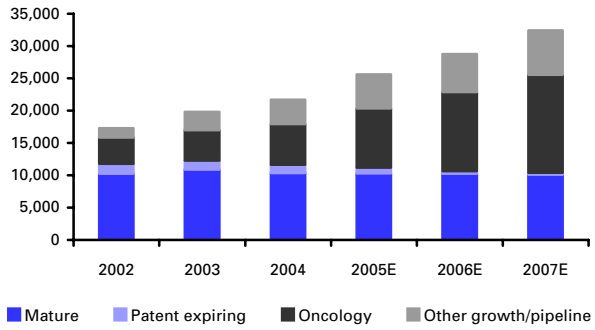
Figure 315: Key expiries and launches 2004-07E

Patent expiries	2004 US Sales	% Pharma	Expiry date
Rocephin	CHF 796m	4%	2005

New product	Peak sales	Indication	Launch date
Avastin	>$2,000m	Colorectal cancer	2004
Tarceva	$800m	Lung cancer	2004
Boniva	$500m	Osteoporosis	2005
CERA	>$1,000m	Anaemia	2007
Lucentis	$500m	AMD	2007

Source: Deutsche Bank and Company information

Figure 316: Portfolio shift 2002-07E (CHF m)



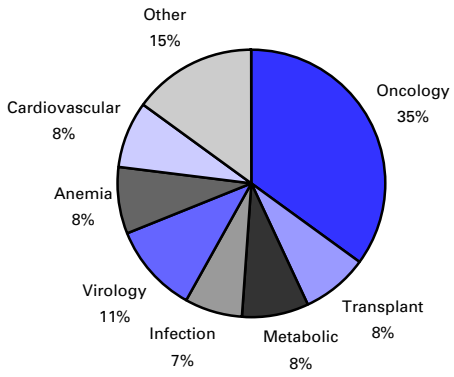
Source: Deutsche Bank and Company information

Figure 317: Summary P&L (CHF m)

	2002	2003	2004E	2005E	2006E	2007E	CAGR
Sales	26,066	27,190	29,523	34,233	38,265	42,733	10.4%
Of which pharma	18,872	19,781	21,696	26,043	29,460	33,204	12.0%
COGS	(5,984)	(6,097)	(7,718)	(9,070)	(9,856)	(10,656)	12.2%
SG&A	(9,052)	(9,177)	(10,423)	(11,557)	(12,077)	(12,884)	7.3%
R&D	(4,132)	(4,624)	(5,154)	(5,451)	(6,025)	(6,591)	9.8%
EBIT	5,223	5,793	6,766	8,585	10,794	13,150	20.3%
EBITDA	7,532	8,038	9,047	10,994	13,255	15,647	15.7%
'Core' EPS	3.96	4.79	6.30	7.51	9.40	11.40	23.5%
COGS %	*23.0%*	*22.4%*	*26.1%*	*26.5%*	*25.8%*	*24.9%*	*1.7%*
SG&A %	*34.7%*	*33.8%*	*35.3%*	*33.8%*	*31.6%*	*30.2%*	*-2.8%*
R&D %	*15.9%*	*17.0%*	*17.5%*	*15.9%*	*15.7%*	*15.4%*	*-0.5%*
EBIT %	*20.0%*	*21.3%*	*22.9%*	*25.1%*	*28.2%*	*30.8%*	*9.0%*

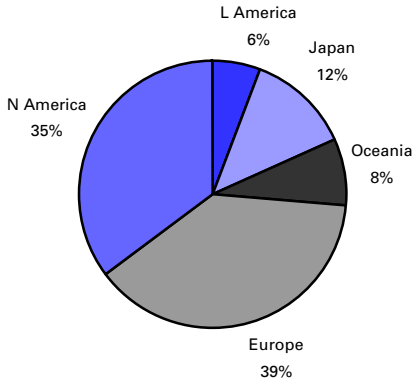
Source: Deutsche Bank and Company information

Figure 318: Sales by therapeutic category 2004



Source: Company information

Figure 319: Sales by geography 2004



Source: Company information

Figure 320: Key pharmaceutical products (sales in CHF m)

Brand	Generic	Lead Indication	US Patent	US Exclusivity	Sales 2004	Sales 2008E
Bacterial infections						
Rocephin	ceftriaxone	Antibiotic	Jul-05	n.a.	1302	196
Oncology						
Rituxan/MabThera	rituximab	NHL	Biologic	Biologic	3378	6076
Furtulon	doxifluridine	Breast cancer	Non-US	Non-US	194	155
Xeloda	capecitabine	Colorectal cancer	Jan-11	Apr-04	541	1212
Herceptin	trastuzumab	Breast cancer	Biologic	Biologic	1435	4436
Kytril	granesetron	Emesis	Dec-07	Expired	457	385
Tarceva	erlotinib	Lung cancer	2017	Nov-09	17	1002
Avastin	bevacizumab	Colorectal cancer	Biologic	Biologic	690	5183
Neutrogin/Neupogen	lenograstim	Neutropaenia	Non-US	Non-US	322	296
NeoRecormon/Epogin	erythropoeitin	Anaemia	Non-US	Non-US	2082	2057
CERA	erythropoeitin	Anaemia	n.a.	n.a.	0	833
Virology						
Invirase/Fortovase	saquinivir	HIV	Nov-10	Expired	143	122
Roferon-A	Interferon alpha	Hepatitis C	Biologic	Biologic	144	99
Cymevene/Valcyte	ganciclovir	CMV retinitis	Jul-14	Expired	329	429
Viracept	nelfinavir	HIV	Non-US	Non-US	234	194
Tamiflu	oseltamivir	Influenza	Dec-16	Expired	330	615
Pegasys	pegylated interferon	Hepatitis C	Biologic	Biologic	1562	2690
Fuzeon	pentafuside	HIV	Jun-13	Mar-08	168	369
Cardiovascular						
Activase/TNKase	alteplase/tenctaplase	MI	Biologic	Biologic	277	266
Dilatrend	carveldilol	CHF/Hypertension	Non-US	Non-US	361	255
Dermatology						
Roaccutane	isotretinoin	Acne	Expired	Expired	316	157
Raptiva	efalizumab	Psoriasis	Biologic	Biologic	70	155
Metabolism						
Protropin/Nutropin	somatropin	Growth hormone deficiency	Biologic	Biologic	448	447
Xenical	orlistat	Obesity	Dec-09	Expired	593	621
Bonviva	ibandronate	Osteoporosis	2012	May-08	0	500
Transplantation						
Cellcept	mycophenolate	Transplantation	May-09	Expired	1396	2254

Source: Company data, Deutsche Bank estimates

NOTES

Europe France
Pharmaceuticals Pharmaceuticals

2 August 2005

Sanofi-Aventis

Reuters: **SASY.PA** Bloomberg: **SAN FP** Exchange: **PAR** Ticker: **SASY.PA**

Patent challenged

Formed in 2004 through the merger of Sanofi-Synthélabo and Aventis, both the offspring of mergers themselves, Sanofi-Aventis now ranks as the third largest pharmaceutical company with a 7% share of the global market. Domiciled in France, the company has significant franchises in cardiovascular disorders, metabolism and oncology and is one of the leading producers of vaccines.

Robust near term growth boosted by merger savings
Following the merger, we forecast Sanofi-Aventis to show strong near term earnings growth, with double-digit sales of key products such as Lovenox (thrombosis), Plavix (thrombosis), Taxotere (cancer), Eloxatin (cancer) and Lantus (diabetes) driving solid top line growth, while merger synergies (forecast to total Euro 1.6bn by 2006E) should enhance bottom line performance.

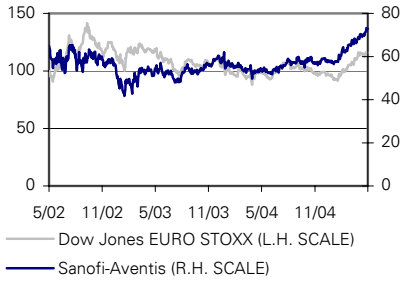
Patent expiries undermine longer term prospects
While much attention has focused on the US patent trial for Plavix (which is co-marketed with Bristol-Myers and accounts for 8% of 2005E developed sales and 11% of EBIT), we note that even if Sanofi retains Plavix in the near term, a series of patent expiries over the 2005-12 timeframe put an estimated 45% of Group EBIT at risk of generic competition. Over the next two years, the company is expected to see US generic competition to allergy drug Allegra (4% of 2005E developed sales) and insomnia drug Ambien (4%), while in the longer term, Sanofi is set to lose US sales of Eloxatin, Taxotere, Copaxone, Plavix and Avapro.

Large pipeline but low visibility
Sanofi's R&D pipeline offers a large and balanced portfolio of new molecules targeting major disease opportunities such as Alzheimer's, depression, obesity and cardiovascular disorders, with many compounds that act via innovative new mechanisms. At the same time, several of these represent high-risk projects or follow-on molecules, while Sanofi's and Aventis' pre-merger track records offer little comfort given previous filing delays, launch disappointments and discontinued projects. Clinical data for many of the mid-stage projects is also limited. The major near term opportunity is obesity drug Acomplia which is expected to be launched in 2006 and could top $1bn in peak sales.

Hold

Price at 2 August 2005 (EUR)	**71.20**
Price Target (EUR)	**69.00**
52-week range (EUR)	**73.15-51.80**

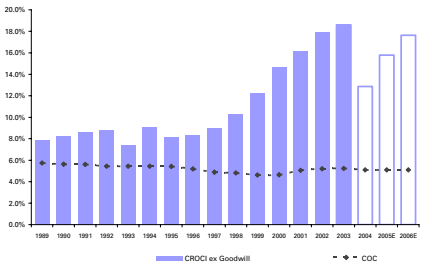
Price/price relative



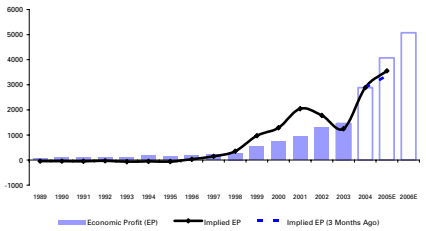
Stock data

Market cap (EUR bn)	**93.1**
Shares outstanding (m)	**1,335**
Free float (%)	**100**
Key shareholders	**TOTAL 13%**
	L'Oreal 10%

Returns ex-Goodwill vs Cost of Capital



Economic/Discounted Economic Profit



Forecasts and ratios

Year End Dec 31	2003A	**2004A**	2005E	2006E	2007E
Revenue (EUR m)	8,048	25,199	27,653	29,626	30,358
EBITA (EUR m)	2,946	3,712	5,265	6,324	6,429
DB PBT (EUR m)	3,149	6,942	8,655	9,816	10,081
DB EPS (EUR)	3.00	3.77	4.62	5.21	5.34
P/E (DB EPS) (x)	17.4	14.8	15.0	13.3	13.0
EV/EBITA (x)	11.5	22.9	19.0	15.2	14.3
DPS (EUR)	0.97	1.20	1.45	1.64	1.71
Yield (%)	1.9	2.1	2.1	2.4	2.5

Source: Deutsche Bank

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Figure 321: Key expiries and launches 2004-07E

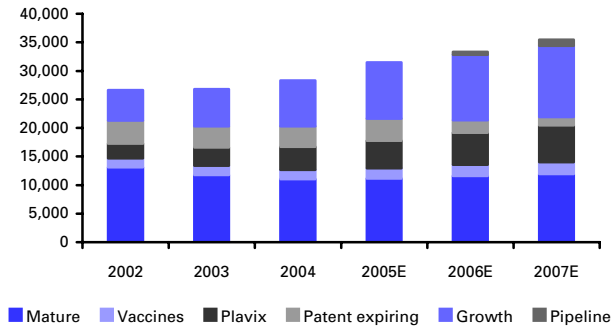
Patent expiries	2004 US Sales	% Developed sales	Expiry date
Amaryl	Euro 216m	1%	2005
Ambien	Euro 1,164m	4%	2006
Allegra	Euro 1,197m	4%	2006*

New product	Peak sales	Indication	Launch date
Ketek (US)	$1,500m	Bacterial infection	2004
Ambien CR	$500m	Insomnia	2005
Menactra	$600m	Meningitis (vaccine)	2005
Apidra	$250m	Diabetes	2006
Alvesco	$1,000m	Asthma	2006
Acomplia	$800m	Obesity	2006
Exubera	$1,000m	Diabetes	2006
dronedarone	$300m	Arrhythmia	2006

**Assumes litigation unsuccessful*

Source: Deutsche Bank and Company information

Figure 322: Portfolio shift, proforma 'developed' sales



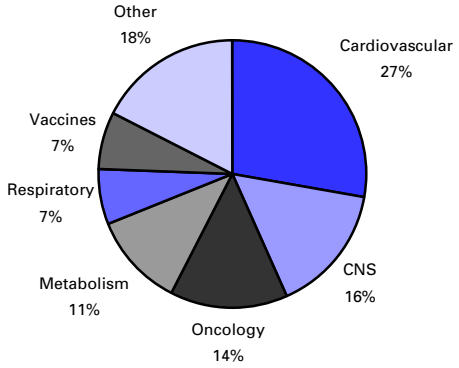
Source: Deutsche Bank and Company information

Figure 323: Summary P&L (Euro m)

	2003	2004E	2005E	2006E	2007E	CAGR
Sales	24,296	25,199	27,653	29,626	30,358	5.7%
COGS	(5,783)	(6,918)	(7,265)	(7,752)	(8,154)	9.0%
SG&A	(7,515)	(7,888)	(8,282)	(8,655)	(8,915)	4.4%
R&D	(4,068)	(3,964)	(4,301)	(4,516)	(4,742)	3.9%
EBIT	7,130	7,640	9,193	10,252	10,357	9.8%
EBITDA	8,283	8,504	10,132	11,273	11,470	8.5%
EPS, adjusted	3.29	3.77	4.62	5.21	5.34	12.8%
COGS %	*23.8%*	*27.5%*	*26.3%*	*26.2%*	*26.9%*	*3.1%*
SG&A %	*30.9%*	*31.3%*	*30.0%*	*29.2%*	*29.4%*	*-1.3%*
R&D %	*16.7%*	*15.7%*	*15.6%*	*15.2%*	*15.6%*	*-1.7%*
EBIT %	*29.3%*	*30.3%*	*33.2%*	*34.6%*	*34.1%*	*3.8%*

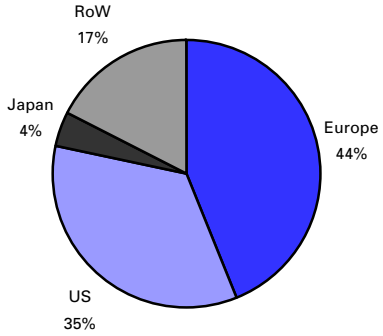
Source: Deutsche Bank and Company information

Figure 324: Sales by category, proforma 2004



Source: Company information

Figure 325: Sales by geography 2004



Source: Company information

Figure 326: Key pharmaceutical products (sales in Euro m)

Brand	Generic	Lead Indication	US patent	US Exclusivity	Sales 2004*	Sales 2008E*
Cardiovascular						
Avapro/Aprovel	irbesartan	Hypertension	Sep-11	Expired	788 (1437)	1112 (1954)
Plavix	clopidrogel	Thrombosis	Nov-11	Expired	1670 (4084)	2888 (6949)
Lovenox	enoxaparin	Thrombosis	Feb-12	Expired	1892	2902
Delix/Tritace	ramipril	Hypertension	Non-US	Non-US	969	851
n.a.	dronedarone	Arrhythmia	n.a.	n.a.	0	150
Central nervous system						
Ambien/Stilnox	zolpidem	Insomnia	Oct-06	Expired	1388	351
Ambien CR	zolpidem	Insomnia	n.a.	n.a.	0	414
Depakine	valproate	Epilepsy	Non-US	Non-US	301	348
SR 58611	n.a.	Depression	n.a.	n.a.	0	150
Oncology						
Eloxatin	oxaliplatin	Colorectal cancer	Expired	Aug-07***	1203	1637
Taxotere	docetaxel	Breast/lung cancer	May-10	Expired	1434	2004
Respiratory						
Allegra	fexofenadine	Allergic rhinitis	Expired	Expired	1503	468
Alvesco	ciclesonide	Asthma	n.a.	n.a.	0	220
Metabolism						
Lantus	insulin glargine	Diabetes	Mar-15	Oct-05	832	2053
Amaryl	glimepiride	Diabetes	Oct-05	Expired	677	576
Apidra	insulin glulisine	Diabetes	n.a.	n.a.	0	125
Acomplia	rimonabant	Obesity	n.a.	n.a.	0	950
Other						
Copaxone	glatiramer	Multiple sclerosis	Jan-08**	Expired	732	377
Actonel (P&G co-promo)	risedronate	Osteoporosis	Dec-13	Expired	305 (1090)	616 (1985)
Nasacort	triamcinolone	Asthma	Jul-16	Expired	287	142
Xatral/Uroxatral	alfuzosin	BPH	Expired	Jun-08***	276	377
Ketek	telithromycin	Antibiotic	Sep-15	Apr-09	189	406
Vaccines	n.a.	Various	n.a.	n.a.	1624	2191

*Source: Company data, Deutsche Bank estimates *Bracketed numbers represent global "developed" sales for Plavix and Avapro through alliance with BMS and global sales for Actonel through agreement with Proctor & Gamble. **US rights returned to Teva ***Composition of matter patent expired. Expect first generic filing one year ahead of NCE expiry, triggering 30 month Hatch Waxman stay.*

NOTES

Europe Germany
Pharmaceuticals Pharmaceuticals

2 August 2005

Schering

Reuters: **SCHG.DE** Bloomberg: **SCH GY** Exchange: **GER** Ticker: **SCHG.DE**

In calm waters

Schering is a German pharmaceutical and diagnostics company that boasts a collection of strong franchises in niche markets. In particular, it holds leading positions in pharmaceutical markets for the treatment of multiple sclerosis, fertility control and hormone replacement therapy while also being the dominant producer of diagnostic media for use in MRI, X-ray and ultrasound. Schering also owns a dermatology business, Intendis, for which it is seeking a partner.

Pipeline needs more time after setbacks

After several pipeline setbacks (five US approvable letters in a row) Schering's late-stage therapeutics pipeline appears unspectacular, which makes a premium rating highly unlikely in our view. Schering is working on some interesting early-stage cancer compounds (such as ZK-RPO or ZK-CDK), but it will most likely take until 2007 before meaningful data could be released. Yaz (contraception) and Angeliq (HRT) might be approved by year-end 2005, which should support growth in 2006/07.

Solid near-term financials

We forecast 6% sales and 15% EPS CAGR for 2004-07E, which is largely independent of new product launches or other risky assumptions. We have never seen a management team at Schering so serious on costs (the company launched an aggressive 'FOCUS' initiative in 2004) so we feel confident with our ambitious earnings estimates, and believe Schering can achieve an 18.8% EBIT margin in 2006E (the company has guided for 18%) with scope for further improvements due to mix, scale and restructuring measures.

Shares seem fairly valued

Over the medium term, Schering's investment case needs more pipeline promise, especially as the company's two largest products may come under pressure. Specifically, multiple sclerosis treatment Betaseron could face biogenerics and new oral treatments alternatives in 2-3 years time, while the patent challenge for oral contraceptive Yasmin remains a considerable risk as well. Thus, despite Schering's superior near-term earnings growth, the company's inferior pipeline prospects suggest the shares merit a slight discount to the sector in our view.

Forecasts and ratios

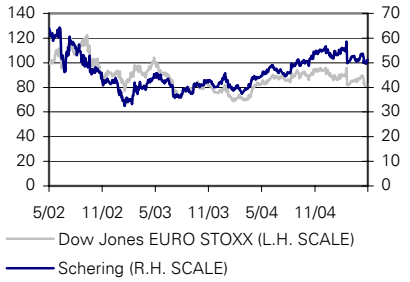
Year End Dec 31	2001A	**2002A**	2003E	2004E	2005E
Revenue (EUR m)	4,828	4,907	5,209	5,526	5,902
EBITA (EUR m)	733	761	891	1,033	1,150
Stated PBT (EUR m)	701	752	917	1,032	1,148
Stated EPS (EUR)	2.28	2.62	3.14	3.60	4.00
P/E (DB EPS) (x)	15.9	17.6	16.1	14.1	12.6
EV/EBITA (x)	10.5	11.3	10.3	8.7	7.7
DPS (EUR)	0.93	0.93	1.24	1.42	1.58
Yield (%)	2.3	2.0	2.4	2.8	3.1

Source: Deutsche Bank

Hold

Price at 2 August 2005 (EUR)	**52.36**
Price Target (EUR)	**54.00**
52-week range (EUR)	**58.56-44.47**

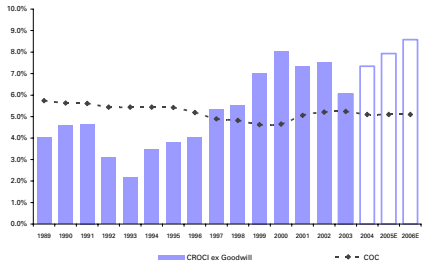
Price/price relative



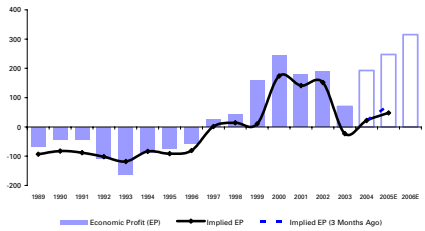
Stock data

Market cap (EUR bn)	**9.6**
Shares outstanding (m)	**190**
Free float (%)	**90**

Returns ex-Goodwill vs Cost of Capital



Economic/Discounted Economic Profit



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Figure 327: Key expiries and launches 2004-07E

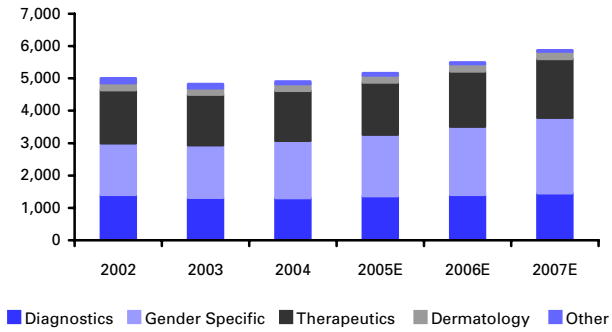
Patent expiries	2004 US Sales	% Pharma	Expiry date
Yasmin	Euro 211m	6%	2007*

New product	Peak sales	Indication	Launch date
Angeliq (US)	$300m	HRT	2005/6
Yaz (Yasmin 20)	$200m	Contraception	2005/6
asoprisnil	$200m	Uterine fibroids	2006

**If litigation successful*

Source: Deutsche Bank and Company information

Figure 328: Portfolio shift (2002-07E, Euro m)



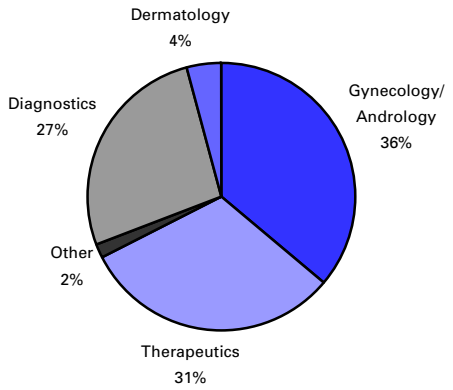
Source: Deutsche Bank and Company information

Figure 329: Summary P&L (Euro m)

	2002	2003	2004E	2005E	2006E	2007E	CAGR
Sales	5,023	4,828	4,907	5,209	5,526	5,897	3.3%
Of which pharma	3,449	3,516	3,599	3,831	4,111	4,435	5.2%
COGS	1,212	1,233	1,206	1,245	1,271	1,326	1.8%
SG&A	2,195	2,091	2,072	2,170	2,288	2,418	2.0%
R&D	947	924	919	958	995	1,044	2.0%
EBIT	741	686	761	891	1,033	1,149	9.2%
EBITDA	1,015	963	1,032	1,163	1,305	1,420	6.9%
EPS (euro)	2.35	2.28	2.62	3.14	3.60	4.00	11.2%
COGS %	*24.1%*	*25.5%*	*24.6%*	*23.9%*	*23.0%*	*22.5%*	*-1.4%*
SG&A %	*43.7%*	*43.3%*	*42.2%*	*41.7%*	*41.4%*	*41.0%*	*-1.3%*
R&D %	*18.9%*	*19.1%*	*18.7%*	*18.4%*	*18.0%*	*17.7%*	*-1.3%*
EBIT %	*14.8%*	*14.2%*	*15.5%*	*17.1%*	*18.7%*	*19.5%*	*5.7%*

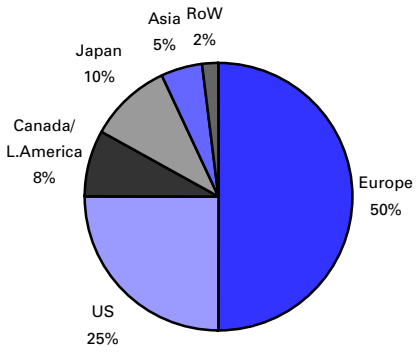
Source: Deutsche Bank and Company information

Figure 330: Sales by category 2004



Source: Company information

Figure 331: Sales by geography 2004



Source: Company information

Figure 332: Key pharmaceutical products (sales in Euro m)

Brand	Generic	Indication	US patent	US Exclusivity	Sales 2004	Sales 2008E
Contraception/HRT						
Diane	cyproterone/ethinylestradiol	Contraception	Non-US	Non-US	186	146
Microgynon	levonorgestrel/ethinylestradiol	Contraception	Non-US	Non-US	128	113
Mirena	levonorgestrol	Contraception	Non-US	Non-US	199	297
Angeliq	drosperinone/estradiol	HRT	n.a.	n.a.	14	250
Yasmin	drospirenone/ethinylestradiol	Contraception	2013/2020*	Expired	429	808
Inflammation						
Betaseron	beta interferon	Multiple sclerosis	Biologic	Biologic	782	998
Oncology						
Fludara	fludarabine	CLL	Expired	Expired	103	28
Campath	alemtuzumab	CLL	Biologic	Biologic	97	209
Zevalin	ibritumomab	NHL	Biologic	Biologic	15	46
Androcur	cyproteron	Prostate cancer	Non-US	Non-US	81	58
Leukine	sargramostim	Neutropaenia	Biologic	Biologic	100	100
Bonefos	sodium clodronate	Hypercalcaemia	Non-US	Non-US	51	50

Source: Company data, Deutsche Bank estimates **No composition of matter patent. Listed patents cover formulation and method of use.*

NOTES

North America United States
Health Care Pharmaceuticals/Major

2 August 2005

Bristol-Myers Squibb

Reuters: **BMY.N** Bloomberg: **BMY UN** Exchange: **NYSE** Ticker: **BMY.N**

Challenging times: Shares trade as a bond, on div yield

Bristol-Myers Squibb derives nearly 80% of its sales from pharmaceuticals with strong franchises in cardiovascular, oncology and anti-infective markets. Aside from prescription drugs, the company has solid positions in consumer health, imaging agents, wound care and infant nutritionals.

Accounting issues resolved but patent expiries undermine growth
Although the unwinding of stuffed wholesaler channels and the restatement of historical financial statements is now firmly behind the company, the near term earnings outlook remains uninspiring as the company faces US patent expiries on several key products including its best-selling cholesterol lowering drug Pravachol (2005E US sales $1bn). Importantly, these exclusivity losses, the need to maintain marketing spend in support of key products, launches and R&D projects and the need to maintain the dividend have forced Bristol-Myers not only to focus more on specialty markets, but also to pursue disadvantageous deals such as its co-marketing agreement with Merck for muraglitazar.

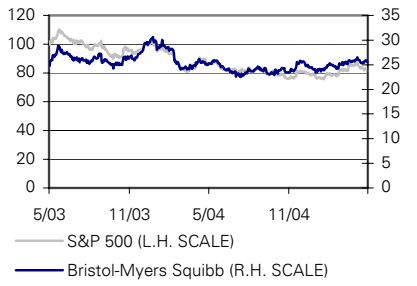
Pipeline launches should support return to growth in 2007
Despite Bristol-Myers' lackluster earnings profile, the shares have earned a premium rating due to the high dividend yield and growing enthusiasm over the late stage pipeline. Indeed, recent launches including Abilify (schizophrenia), Erbitux (colorectal cancer) and Reyataz (HIV) have all seen strong uptake and are forecast to comprise 20% of sales in 2007E. In addition, Bristol-Myers expects to enter the rapidly growing market for biological treatments for rheumatoid arthritis (worth over $8bn in 2005E) with abatacept, while it also hopes to reinvigorate its diabetes franchise with the first dual-acting insulin sensitizer muraglitazar. However, on muraglitizar, an FDA review is scheduled for September 2005 and we expect approval will be delayed into 2007.

Dividend yield and takeover speculation likely to support valuation
The compromised operational and financial leverage resulting from the patent pressures and strategic challenges facing the company suggests it is vulnerable to a takeover. However, this remains unlikely, in our view, before a ruling in the Plavix litigation as US sales of the drug account for $0.45 of Bristol-Myers' current earnings. Nevertheless, we believe the company's attractive dividend yield (4.5%) limits the downside near term, but would have to be cut in the event of a loss of in the Plavix litigation.

Hold

Price at 2 August 2005 (USD)	**25.04**
Price target	**25.00**
52-week range	**26.48-22.50**

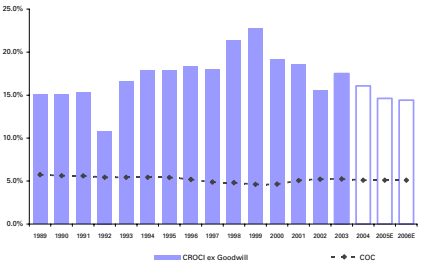
Price/price relative



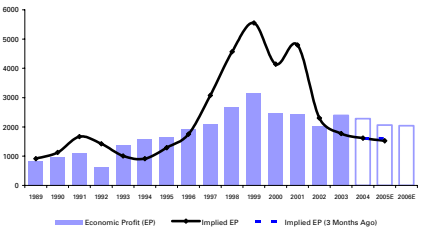
Stock data

Market cap (USD bn)	**49.3**
Shares outstanding	**1,941.4**
Free float (%)	**100**

Returns ex-Goodwill vs Cost of Capital



Economic/Discounted Economic Profit



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Forecasts and ratios

Year End Dec 31	2003A	2004A	2005E	2006E	2007E
Revenue (USDm)	18,653	19,380	19,364	19,692	21,042
DB PBT (USD m)	4,982	4,892	4,450	4,271	4,625
FY EPS (USD)	1.75	1.69	1.44	1.32	1.45
P/E (x)	14.4	14.9	17.3	18.9	17.2
Dividend yield (%)	4.5	4.5	4.7	5.0	5.0

Source: Deutsche Bank

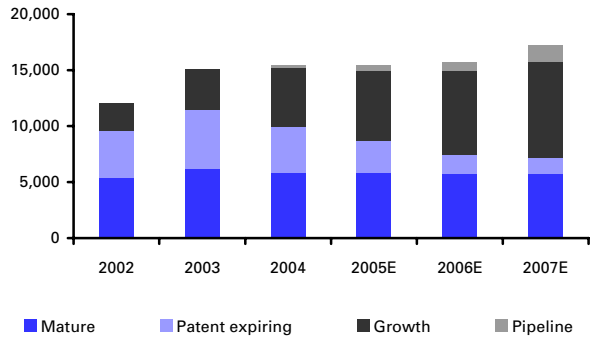
Figure 333: Key expiries and launches 2004-07E

Patent expiries	2004 US Sales	% Pharma	Expiry date
Glucophage XR	$67m	<1%	2004
Glucovance	$165m	1%	2004
Paraplatin	$537m	3%	2004
Cefzil	$161m	1%	2005
Pravachol	$1,426m	9%	2006
Videx	$105m	1%	2007

New product	Peak sales	Indication	Launch date
Erbitux	$700m	Colorectal cancer	2004
Baraclude	$500m	Hepatitis B	2005
abatacept	$750m	Rheumatoid arthritis	2005
muraglitazar	>$1,000m	Diabetes	2007
ixabepilone	$500m	Cancer	2007

Source: Deutsche Bank and Company information

Figure 334: Portfolio shift 2002-07E ($m)



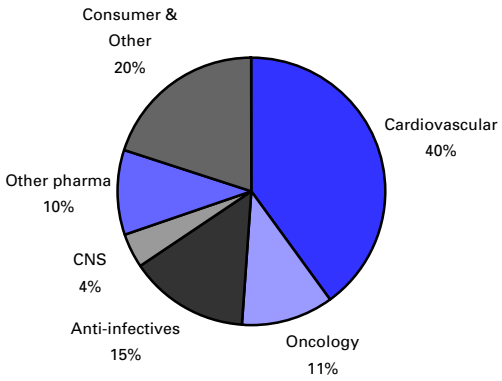
Source: Deutsche Bank and Company information

Figure 335: Summary P&L ($m)

	2002	2003	2004E	2005E	2006E	2007E	CAGR
Sales	16,208	18,653	19,380	19,314	19,692	21,042	5.4%
Of which pharma	12,057	15,092	15,482	15,319	15,547	15,547	5.2%
COGS	(4,690)	(5,406)	(5,989)	(5,921)	(6,301)	(6,691)	7.4%
SG&A	(5,224)	(6,064)	(6,265)	(6,403)	(6,380)	(6,796)	5.4%
R&D	(2,206)	(2,177)	(2,446)	(2,725)	(3,000)	(3,200)	7.7%
EBIT	4,101	5,006	4,680	4,265	4,011	4,355	1.2%
EBITDA	4,786	5,745	5,539	5,215	5,086	5,505	2.8%
EPS ($)	1.38	1.75	1.69	1.44	1.32	1.45	1.0%
COGS %	*28.9%*	*29.0%*	*30.9%*	*30.7%*	*32.0%*	*31.8%*	1.9%
SG&A %	*32.2%*	*32.5%*	*32.3%*	*33.2%*	*32.4%*	*32.3%*	0.0%
R&D %	*13.6%*	*11.7%*	*12.6%*	*14.1%*	*15.2%*	*15.2%*	2.2%
EBIT %	*25.3%*	*26.8%*	*24.1%*	*22.1%*	*20.4%*	*20.7%*	-3.9%

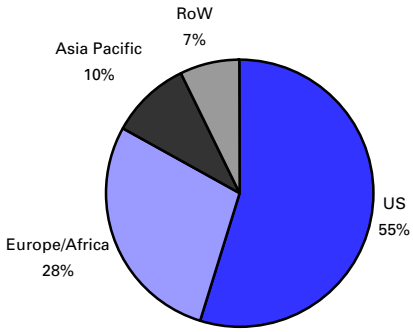
Source: Deutsche Bank and Company information

Figure 336: Group sales by category 2004



Source: Company information

Figure 337: Sales by geography 2004



Source: Company information

Figure 338: Key pharmaceutical products (sales in $m)

Brand	Generic	Lead Indication	Key US Patents	US Exclusivity	Sales 2004	Sales 2007E
Cardiovascular						
Pravachol	pravastatin	Cholesterol	Apr-06	Expired	2635	850
Plavix	clopidrogel	Anti-thrombotic	Nov-11	Expired	3327	4675
Avapro	irbesartan	Hypertension	Sep-11	Expired	930	935
Monopril	fosinopril	Hypertension	Expired	Expired	274	224
Coumadin	warfarin	Stroke prevention	Expired	Expired	255	180
Oncology						
Taxol	paclitaxel	Lung/breast cancer	Expired	Expired	991	601
Erbitux	cetuximab	Colorectal cancer	Biologic	Biologic	261	575
Paraplatin	carboplatin	Lung cancer	Expired	Expired	673	100
Anti-infectives						
Zerit	stavudine	HIV	Dec-08	Expired	272	250
Sustiva	evafirenz	HIV	Sep-14	Expired	621	815
Videx	didanosine	HIV	Mar-07	Expired	274	190
Reyataz	atazanavir	HIV	Apr-17	Jul-08	414	1300
Baraclude	entecavir	Hepatitis B	Oct-10	Mar-10	0	350
Cefzil	cefprozil	Antibiotic	Dec-05	Expired	271	130
Tequin	gatifloxacin	Antibiotic	Dec-07	Expired	169	95
Metabolism						
Glucophage (incl. XR)	metformin	Diabetes	Expired	Expired	135	55
Glucovance	metformin/glyburide	Diabetes	Expired	Expired	170	11
Metaglip	metformin/glipizide	Diabetes	Expired	Oct-05	32	45
Pargluva	muraglitazar	Diabetes	n.a.	n.a.	0	250
Other						
Abilify	aripiprazole	Schizophrenia	2014*	Nov-07	594	1670
Orencia	abatacept	Rheumatoid arthritis	n.a.	n.a.	0	350

*Source: Company data, Deutsche Bank estimates *Assumes patent term extension*

NOTES

North America United States
Health Care Pharmaceuticals/Major

2 August 2005

Eli Lilly

Reuters: **LLY.N** Bloomberg: **LLY UN** Exchange: **NYSE** Ticker: **LLY.N**

Zyprexa remains on a slippery slope

Eli Lilly is a global pharmaceutical manufacturer with core franchises in central nervous system disorders, diabetes/endocrinology, anti-infectives and oncology. The animal health division (Elanco) comprises 6% of sales.

Zyprexa sales slowing and still the biggest contributor to earnings
Sales of Lilly's antipsychotic Zyprexa reached $4.4bn and accounted for 34% of Lilly's pharma sales in 2004. However, increased competition in the schizophrenia market together with concerns over the increased risk of diabetes associated with Zyprexa have led to a decline in US sales over the past two years. Although strong performance in international markets has offset the US weakness thus far, this source of growth is also showing signs of deceleration. As we estimate that Zyprexa sales account for roughly half of Lilly's earnings, a significant component of future growth will be dependent on the level at which Zyprexa's share stabilises in the US market as well as any shift in international performance.

Pipeline amongst best in industry…
Lilly is often cited as having one of the best R&D pipelines in the industry with a number of high potential products in Phase II and Phase III development. Key amongst the near term opportunities are Byetta, a first-in-class GLP-1 analog recently approved by the FDA for the treatment of diabetes; ruboxistaurin, a novel treatment for neuropathic pain with $1bn peak sales potential; and prasugrel, a novel anti-clotting agent that will compete with Sanofi's $4bn drug Plavix.

…but recent launches suggest mixed track record
Inspection of several of Lilly's recent launches reveals a mixed track record. On the one hand, cancer drug Alimta and antidepressant Cymbalta have captured significant market share gains since their approval in 2004, while on the other hand, sales of attention deficit drug Strattera, erectile dysfunction drug Cialis, and sepsis treatment Xigris, quickly plateaued and have generally fallen short of original market expectations. Given the downturn in Zyprexa sales and the slowdown in Lilly's endocrine franchise, however, successful commercialisation of the pipeline will be critical to sustaining longer term earnings growth and justifying Lilly's premium rating.

Forecasts and ratios

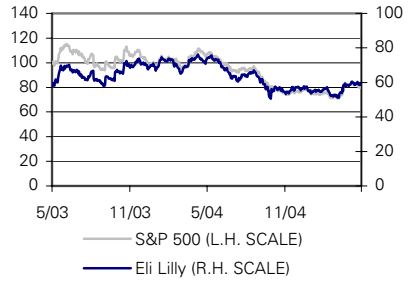
Year End Dec 31	2003A	2004A	2005E	2006E	2007E
Revenue (USDm)	12,583	13,858	14,772	15,760	17,166
DB PBT (USD m)	3,580	3,576	3,948	4,343	4,799
FY EPS (USD)	2.58	2.58	2.83	3.10	3.42
P/E (x)	24.6	25.5	20.0	18.3	16.6
Dividend yield (%)	2.1	2.1	2.8	2.2	2.8

Source: Deutsche Bank

Hold

Price at 2 August 2005 (USD)	**56.69**
Price target	**60.00**
52-week range	**75.66-50.53**

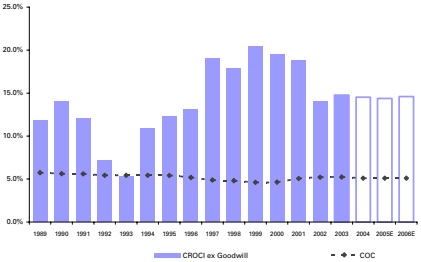
Price/price relative



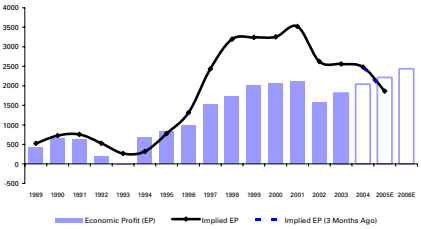
Stock data

Market cap (USD bn)	**61.4**
Shares outstanding	**1,075.6**
Free float (%)	**100**

Returns ex-Goodwill vs Cost of Capital



Economic/Discounted Economic Profit



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Figure 339: Key expiries and launches 2004-07E

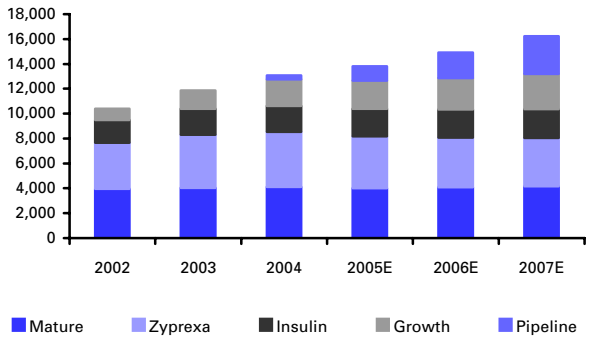
Patent expiries	2004 US Sales	% Pharma	Expiry date
Actos	$340m	2%	2006*

New product	Peak sales	Indication	Launch date
Cymbalta	$1,500m	Depression	2004
Alimta	$750m	Lung cancer	2004
Yentreve	$750m	SUI	2004 (EU)
Byetta	$750m	Diabetes	2005
ruboxistaurin	$1,000m	Diabetic neuropathy	2006
prasugrel	$1,000m	Thrombosis	2007

**US rights returned*

Source: Deutsche Bank and Company information

Figure 340: Portfolio shift 2002-07E ($m)



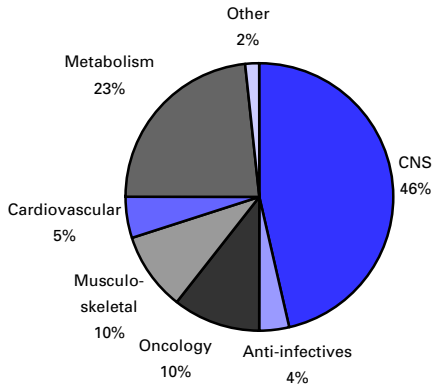
Source: Deutsche Bank and Company information

Figure 341: Summary P&L ($m)

	2002	2003	2004E	2005E	2006E	2007E	CAGR
Sales	11,078	12,583	13,858	14,772	15,760	17,166	9.2%
COGS	(2,177)	(2,675)	(3,246)	(3,552)	(3,767)	(4,103)	13.5%
SG&A	(3,424)	(4,055)	(4,508)	(4,541)	(4,681)	(5,064)	8.1%
R&D	(2,149)	(2,350)	(2,807)	(3,025)	(3,200)	(3,400)	9.6%
EBIT	3,328	3,503	3,297	3,654	4,113	4,599	6.7%
EBITDA	3,821	4,051	3,895	4,304	4,813	5,344	6.9%
EPS ($)	2.55	2.58	2.58	2.83	3.10	3.42	6.0%
COGS %	*19.6%*	*21.3%*	*23.4%*	*24.0%*	*23.9%*	*23.9%*	*4.0%*
SG&A %	*30.9%*	*32.2%*	*32.5%*	*30.7%*	*29.7%*	*29.5%*	*-0.9%*
R&D %	*19.4%*	*18.7%*	*20.3%*	*20.5%*	*20.3%*	*19.8%*	*0.4%*
EBIT %	*30.0%*	*27.8%*	*23.8%*	*24.7%*	*26.1%*	*26.8%*	*-2.3%*

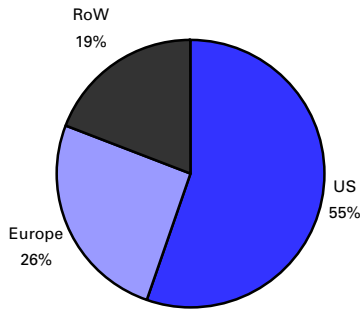
Source: Deutsche Bank and Company information

Figure 342: Sales by therapeutic category 2004



Source: Company information

Figure 343: Sales by geography 2004



Source: Company information

Figure 344: Key pharmaceutical products (sales in $m)

Brand	Generic	Lead Indication	Key US Patents	US Exclusivity	Sales 2004	Sales 2007E
Anti-Infectives						
Ceclor	cefaclor	Antibiotic	Expired	Expired	138	90
Xigris	drotrecogin	Sepsis	Biologic	Biologic	202	290
Vancocin	vancomycin	Antibiotic	Expired	Expired	199	0
Cardiovascular						
ReoPro	abciximab	Thrombosis	Biologic	Biologic	362	350
Oncology						
Alimta	pemetrexed	Lung cancer	Sep-11	Feb-09	143	775
Gemzar	gemcitabine	Lung cancer	May-10	Expired	1214	1580
Endocrinology						
Humatrope	insulin	Diabetes	Biologic	Biologic	430	440
Humulin	insulin	Diabetes	Biologic	Biologic	998	980
Humalog	insulin lispro	Diabetes	Biologic	Biologic	1101	1320
Actos (US co-promo)	pioglitazone	Diabetes	Sep-06*	Jul-04	452	595
Byetta	exenatide	Diabetes	n.a.	Apr-10	0	350
n.a.	ruboxistaurin	Diabetic retinopathy	n.a.	n.a.	0	300
Bone & Inflammation						
Forteo	teriparatide	Osteoporosis	Expired	Nov-05	239	700
Evista	raloxifene	Osteoporosis	Mar-14	Expired	1013	1070
Central Nervous System						
Strattera	atomoxetine	ADHD	May-08	Nov-07	666	485
Cymbalta	duloxetine	Depression	Dec-08	Aug-09	94	1400
Prozac	fluoxetine	Depression	Expired	Expired	558	375
Zyprexa	olanzapine	Schizophrenia	Apr-11	Expired	4420	4050
Other						
Cialis (WW co-promo)	tadalafil	Erectile dysfunction	Jan-16	Nov-08	552**	1120**

*Source: Company data, Deutsche Bank estimates *US rights returned to Takeda **Includes non-consolidates ales through Lilly/ICOS joint venture.*

NOTES

North America United States
Health Care Pharmaceuticals/Major

2 August 2005

Merck & Co.

Reuters: **MRK.N** Bloomberg: **MRK UN** Exchange: **NYSE** Ticker: **MRK.N**

Vioxx aftermath: Shares trade on merit of 4.9% yield

Merck & Co is a global, research-driven pharmaceutical company that develops and markets a broad range of human health products. Following the spin-off of its pharmacy benefit management business, Medco, in 2003, the company is now purely focused on pharmaceuticals and has leading franchises in cardiovascular disorders, anti-infectives and vaccines.

Vioxx withdrawal undermines earnings outlook

Merck's shares took a major hit in September 2004 when the company announced the worldwide withdrawal of its $2.5bn painkiller Vioxx, citing an increased risk of cardiovascular events (stroke, heart attack) seen after three years in a colon cancer prevention study. The immediate effect was to strip 25% from earnings forecasts offset by an estimated 5% benefit from cost cutting. However, it further added to Merck's strategic woes which have been compounding over the last few years.

Late-stage failures leaves pipeline thin

In late 2003, Merck announced the discontinuation of two Phase III pipeline products, both of which were targeted at significant markets (depression and diabetes). While one of the failures was anticipated and the other was a surprise, the loss of both left Merck with a thin late-stage pipeline. Moreover the controversy that arose following the Vioxx withdrawal suggests an uninspiring future for Merck's second generation COX-2 Arcoxia. The one bright spot in Merck's R&D portfolio, however, is its vaccine franchise. In addition to novel vaccines against rotavirus and herpes zoster (the virus that causes shingles), Merck has developed a vaccine against human papillomavirus (HPV), a virus which is associated with the majority of cervical cancers and genital warts. Filing of the HPV vaccine, called Gardisil, is anticipated in H2 2005 (ahead of a competing product from GlaxoSmithKline) and could represent a blockbuster opportunity for Merck.

Near term reliance on Zetia/Vytorin

With the 2006 US patent expiry of Merck's best-seller Zocor looming large and the late stage pipeline relatively thin, the continued success of cholesterol-lowering drugs Zetia and Vytorin (developed and marketed by the Schering-Plough/Merck joint venture) is imperative for future growth. This is made ever more important given slowing sales of several of the other key growth drivers including Cozaar and Fosamax. However, the company's 4.9% dividend yield lends strong support to the stock in the low $30's.

Forecasts and ratios

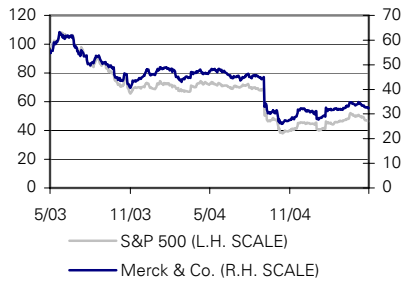
Year End Dec 31	2003A	2004A	2005E	2006E	2007E
Revenue (USDm)	22,484	22,939	21,784	21,093	21,197
DB PBT (USD m)	8,969	7,662	7,693	7,217	7,339
FY EPS (USD)	2.92	2.61	2.47	2.37	2.42
P/E (x)	18.2	16.1	12.6	13.2	12.9
Dividend yield (%)	2.7	3.5	5.3	5.3	5.3

Source: Deutsche Bank

Hold

Price at 2 August 2005 (USD)	**30.68**
Price target	**35.00**
52-week range	**48.37-26.00**

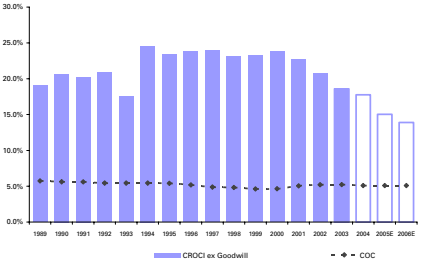
Price/price relative



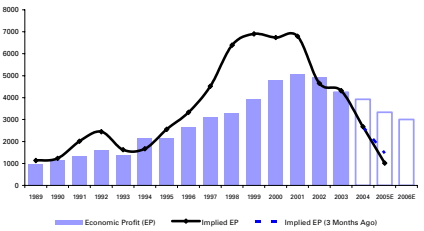
Stock data

Market cap (USD bn)	**69.7**
Shares outstanding	**2,100.0**
Free float (%)	**100**

Returns ex-Goodwill vs Cost of Capital



Economic/Discounted Economic Profit



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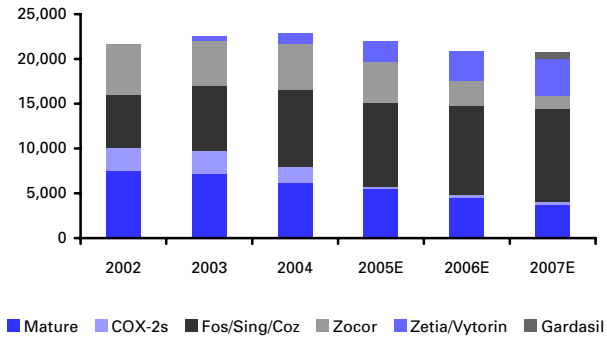
Figure 345: Key expiries and launches 2004-07E

Patent expiries	2004 US Sales	% Pharma	Expiry date
Proscar	$368m	2%	2006
Zocor	3613	16%	2006

New product	Peak sales	Indication	Launch date
Vytorin	>$2,000m	Cholesterol	2004
Gardasil	$1,500m	HPV (vaccine)	2006
Zostavax	$1,000m	Shingles (vaccine)	2006
RotaTeq	$500m	Rotavirus (vaccine)	2006
muraglitazar	>$1,000m	Diabetes	2007
MK-431	$750m	Diabetes	2007

Source: Deutsche Bank and Company information

Figure 346: Portfolio shift 2002-07E* ($m)



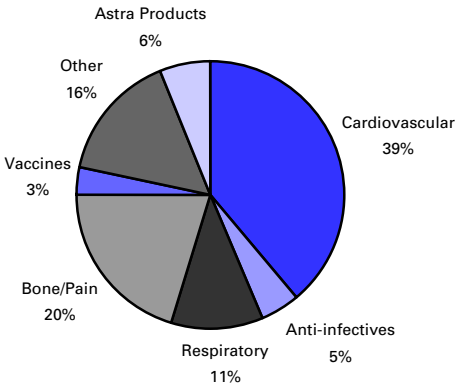
*Source: Deutsche Bank and Company information *Zetia/Vytorin joint venture sales not consolidated*

Figure 347: Summary P&L ($m)

	2002	2003	2004E	2005E	2006E	2007E	CAGR
Sales	21,446	22,484	22,939	21,784	21,093	21,197	-0.2%
COGS	(3,907)	(4,315)	(4,928)	(4,924)	(5,062)	(5,193)	5.9%
SG&A	(5,652)	(6,395)	(7,348)	(6,857)	(6,539)	(6,465)	2.7%
R&D	(2,677)	(3,178)	(3,885)	(3,789)	(3,975)	(4,100)	8.9%
EBIT	9,209	8,595	6,778	6,214	5,517	5,439	-10.0%
EBITDA	10,440	9,909	8,229	7,789	7,217	7,264	-7.0%
EPS ($)	2.99	2.92	2.61	2.47	2.37	2.42	-4.2%
COGS %	*18.2%*	*19.2%*	*21.5%*	*22.6%*	*24.0%*	*24.5%*	*6.1%*
SG&A %	*26.4%*	*28.4%*	*32.0%*	*31.5%*	*31.0%*	*30.5%*	*3.0%*
R&D %	*12.5%*	*14.1%*	*16.9%*	*17.4%*	*18.8%*	*19.3%*	*9.2%*
EBIT %	*42.9%*	*38.2%*	*29.5%*	*28.5%*	*26.2%*	*25.7%*	*-9.8%*

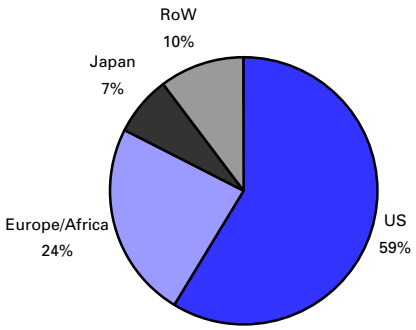
Source: Deutsche Bank and Company information

Figure 348: Sales by therapeutic category 2004*



*Source: Company information *Includes Zetia/Vytorin sales joint venture sales*

Figure 349: Sales by geography 2004



Source: Company information

Figure 350: Key pharmaceutical products (sales in $m)

Brand	Generic	Lead Indication	Key US Patents	US exclusivity	Sales 2004	Sales 2007E
Cardiovascular						
Zocor	simvastatin	Cholesterol	Jun-06	Expired	5196	1350
Cozaar/Hyzaar	losartan	Hypertension	Aug-09	Expired	2824	3350
Zetia (JV with SGP*)	ezetimibe	Cholesterol	Jun-15	Oct-07	1059	2100
Vytorin (JV with SGP*)	ezetimibe/simvastatin	Cholesterol	Jun-15	Oct-07	130	2075
Anti-infectives						
Primaxin	imipenem	Antibiotic	Sep-09	Expired	641	745
Cancidas	caspofungin	Antifungal	Mar-13	Jan-06	430	770
Invanz	ertapenem	Antibiotic	Feb-13	Nov-06	63	220
Crixivan/Stocrin	indinavir	HIV	May-12	Expired	255	455
Other						
Trusopt/Cosopt	dorzolamide	Glaucoma	Oct-08	Expired	559	595
Proscar	finasteride	BPH	Jun-06	Expired	733	320
Fosamax	alendronate	Osteoporosis	Feb-08	Expired	3159	3350
Propecia	finasteride	Alopecia	Jun-06	Expired	270	310
Maxalt	rizatriptan	Migraine	Jun-12	Jun-03	309	350
Singulair	montelukast	Asthma	Aug-12	Aug-03	2622	3950
Emend	aprepitant	Emesis	Jun-12	n.a.	47	160
Arcoxia	etoricoxib	Arthritis	Non-US	Non-US	230	200
Vaccines	n.a.	Various	n.a.	n.a.	753	1430

Source: Company data, Deutsche Bank estimates **Sales consolidated through JV. Share of profits reported as equity income.*

NOTES

North America United States
Health Care Pharmaceuticals/Major

2 August 2005

Pfizer

Reuters: **PFE.N** Bloomberg: **PFE UN** Exchange: **NYSE** Ticker: **PFE.N**

Industry leader with huge financial flexibility

Following the 2003 merger with Pharmacia, Pfizer has cemented its position as the world's largest pharmaceutical company with around 11% of the global market. The healthcare giant generates annual sales upwards of $50bn and boasts strong franchises in cardiovascular, anti-infectives, and CNS disorders. In addition, Pfizer's industry-leading 11,000-person US sales force provides it considerable strength in US marketing. Although setbacks to its COX-2 franchise and generic pressures will make 2005 a 'transition' year, top-line growth combined with aggressive cost savings should drive healthy double-digit earnings growth in 2006 and beyond.

Post Pharmacia merger, Pfizer dwarfs the competition
The merger with Pharmacia in 2003 created a business with enormous potential and financial flexibility. R&D spending of $8 bn p.a. is roughly 50% greater than that of its nearest competitor, while strong growth from the broad healthcare portfolio should be augmented by an aggressive $4bn cost savings programme (announced in April 2005), which comes on top of the $4.2bn of synergies already achieved from the Pharmacia merger.

2005 to be a 'transition' year
Concerns over cardiovascular risk associated with the COX-2 class following the withdrawal of Merck's Vioxx and the FDA's subsequent request for withdrawal of Pfizer's Bextra have reduced revenues from Pfizer's COX-2 franchise by roughly half from peak levels in 2004. This, together with significant generic pressure over the 2004-05 period, has positioned 2005 as a 'transition' year. However, accelerating top-line growth and operational efficiencies should support a return to healthy double-digit earnings growth in 2006 and beyond.

Impact of new competition offset by launch of new products
Pfizer has an impressive launch schedule ahead of it, marked by the planned introduction of new products in the areas of diabetes, insomnia, cancer and osteoporosis, each with sales potential upwards of $500m. In addition, the breadth of its portfolio and strength of its sales force make it a partner of choice for many licensors. However, successful delivery of the pipeline will be critical to sustaining longer term growth as Pfizer compensates for further patent expiries in 2006 and 2007. In addition, positive resolution of the patent challenge to Pfizer's $10bn mega-blockbuster Lipitor (a verdict is expected in 2005) should remove a significant risk overhanging the shares.

Forecasts and ratios

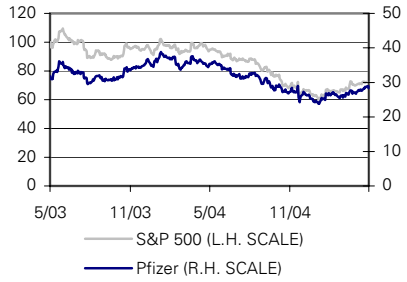
Year End Dec 31	2003A	2004A	2005E	2006E	2007E
Revenue (USDm)	44,738	52,516	52,002	53,633	56,671
DB PBT (USD m)	15,739	20,667	19,121	20,675	22,929
FY EPS (USD)	1.70	2.12	1.99	2.22	2.54
P/E (x)	18.8	15.5	13.6	12.2	10.7
Dividend yield (%)	1.9	2.0	2.8	3.0	3.2

Source: Deutsche Bank

Buy

Price at 2 August 2005 (USD)	**26.64**
Price target	**32.00**
52-week range	**36.14-23.86**

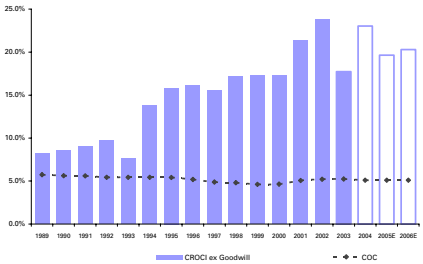
Price/price relative



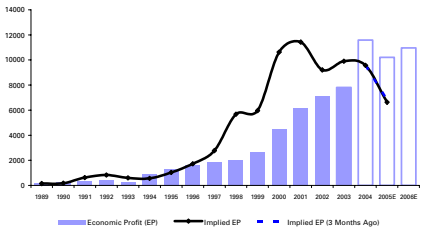
Stock data

Market cap (USD bn)	**202.0**
Shares outstanding	**7,203.0**
Free float (%)	**100**

Returns ex-Goodwill vs Cost of Capital



Economic/Discounted Economic Profit



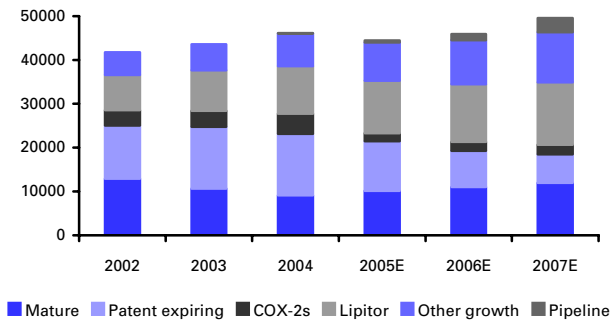
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Figure 351: Key expiries and launches 2004-07E

Patent expiries	2004 US Sales	% Pharma	Expiry date
Accupril	$387m	1%	2004
Diflucan	$417m	1%	2004
Neurontin	$2,198m	5%	2004
Zithromax	$1,393m	3%	2005
Zoloft	$2,657m	6%	2006
Camptosar	$550m	1%	2007
Norvasc	$1,991m	4%	2007
New product	**Peak sales**	**Indication**	**Launch date**
Spiriva	$1,500m	COPD	2004
Lyrica	>$1,000m	Neuropathic pain	2005
Macugen	$500m	AMD	2005
Oporia	$750m	Osteoporosis	2005
indiplon	$750m	Insomnia	2006
Exubera	>$1,000m	Diabetes	2006
Sutent	$750m	Renal cancer	2006
varenicline	$500m	Smoking cessation	2006
maraviroc	$500m	HIV	2007

Source: Deutsche Bank and Company information

Figure 352: Portfolio shift 2002-07E (proforma, $m)



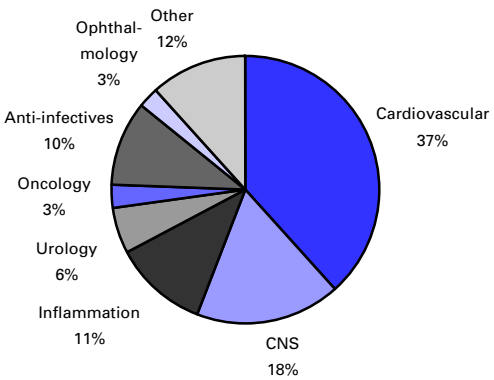
Source: Deutsche Bank and Company information

Figure 353: Summary P&L ($m)

	2002	2003	2004E	2005E	2006E	2007E	CAGR
Sales	32,362	44,738	52,516	52,002	53,633	56,671	11.9%
Of which pharma	28,276	39,425	46,133	45,017	46,323	48,941	11.6%
COGS	(4,059)	(6,849)	(7,503)	(8,775)	(9,654)	(10,541)	21.0%
SG&A	(10,834)	(15,111)	(16,903)	(16,732)	(15,554)	(15,301)	7.1%
R&D	(5,171)	(7,207)	(7,639)	(8,024)	(8,350)	(8,600)	10.7%
EBIT	12,298	15,571	20,471	18,472	20,075	22,229	12.6%
EPS ($)	1.54	1.70	2.12	1.99	2.22	2.54	10.5%
COGS %	*12.5%*	*15.3%*	*14.3%*	*16.9%*	*18.0%*	*18.6%*	*8.2%*
SG&A %	*33.5%*	*33.8%*	*32.2%*	*32.2%*	*29.0%*	*27.0%*	*-4.2%*
R&D %	*16.0%*	*16.1%*	*14.5%*	*15.4%*	*15.6%*	*15.2%*	*-1.0%*
EBIT %	*38.0%*	*34.8%*	*39.0%*	*35.5%*	*37.4%*	*39.2%*	*0.6%*

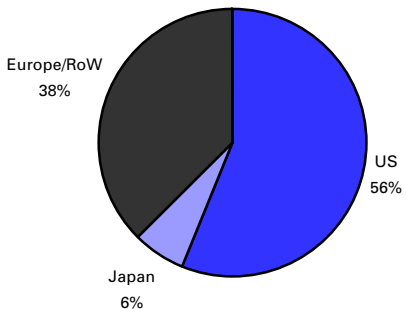
Source: Deutsche Bank and Company information

Figure 354: Pharma sales by therapeutic category 2004



Source: Company information

Figure 355: Sales by geography 2004



Source: Company information

Figure 356: Key pharmaceutical products (sales in $m)

Brand	Generic	Lead Indication	Key US Patents	US exclusivity	Sales 2004	Sales 2007E
Cardiovascular						
Lipitor	atorvastatin	Cholesterol	Mar-10	Expired	10862	14200
Norvasc	amlodipine	Hypertension	Sep-07	Expired	4463	4025
Accupril	quinapril	Hypertension	Expired	Expired	665	250
Cardura XL	doxasocin	Hypertension	Expired	Expired	628	602
Caduet	atorvastatin/amlodopine	Hypertension/cholesterol	Mar-10	Jan-07	50	675
Infection						
Zithromax	azithromycin	Antibiotic	Nov-05	Expired	1851	550
Diflucan	fluconazole	Anti-fungal	Expired	Expired	945	504
Vfend	voriconazole	Anti-fungal	Expired	May-07	287	480
Zyvox	linexolid	Antibiotic	Nov-14	Expired	463	955
Musculoskeletal						
Celebrex	celecoxib	Osteoarthritis	Nov-13	Expired	3302	2200
Oporia	lasofoxifene	Osteoporosis	n.a.	n.a.	0	250
Oncology						
Camptosar	irinotecan	Colorectal cancer	Aug-07	Expired	750	875
Pharmorubicin/Ellence	epirubicin	Breast cancer	Sep-06	Expired	480	305
Sutent	n.a.	Renal cancer	n.a.	n.a.	0	225
CNS						
Zoloft	sertraline	Depression	Jun-06	Expired	3361	1030
Neurontin	gabapentin	Epilepsy	Expired	Expired	2723	500
Lyrica	pregabalin	Epilepsy/Neuropathic pain	Mar-08	Dec-09	0	700
Aricept*	donepezil	Alzheimer's	Nov-10	Expired	308	475
Relpax	eletriptan	Migraine	Aug-13	Dec-07	169	420
n.a.	indilpon	Insomnia	n.a.	n.a.	0	400
Geodon	ziprasidone	Schizophrenia	Mar-07	Feb-07	467	960
Xanax	alprazolam	Anxiety	Expired	Expired	378	395
Diabetes						
Exubera	insulin	Diabetes	n.a.	n.a.	0	500
Other						
Xalatan	timaprost	Glaucoma	Mar-11	Expired	1227	1630
Macugen	pegaptanib	AMD	Jan-17	Dec-09	0	200
Zyrtec/Reactine	cetirizine	Rhinitis	Dec-07	Expired	1287	1450
Viagra	sildenafil	Erectile dysfunction	Jun-11	Expired	1678	2150
Detrol	tolterodine	Urinary incontinence	Sep-12	Expired	904	1120
Genotropin	somatropin	Growth hormone deficiency	Biologic	Biologic	736	1065

Source: Company data, Deutsche Bank estimates **Direct sales booked under alliance with Eisai*

NOTES

North America United States
Health Care Pharmaceuticals/Major

2 August 2005

Schering-Plough

Reuters: **SGP.N** Bloomberg: **SGP UN** Exchange: **NYSE** Ticker: **SGP.N**

Relying on Zetia/Vytorin

Deriving around 80% of its consolidated revenues from ethical pharmaceuticals, Schering-Plough has strong franchises in allergy, respiratory and infectious disease. In addition, through its joint venture with Merck which markets Zetia and Vytorin, the company has a strong presence in the cardiovascular field. Aside from pharmaceuticals, Schering-Plough derives modest revenues from its operations in animal health, foot care (Dr Scholl), sun care (Coppertone) and OTC medicines.

2004 the trough year for earnings
The loss of market exclusivity for its leading anti-histamine Claritin and increasing competitive pressures across the rest of its portfolio led to the collapse of Schering-Plough's earnings over the 2002-2004 period. However, the replacement of former CEO Dick Kogan with ex-Pharmacia head Fred Hassan in 2003 marked a transition at the company. Under new management, the company has undertaken a formal action plan to stabilise the existing franchise, repair the underlying infrastructure and initiate a turnaround.

Mega-blockbuster opportunity for Zetia and Vytorin…
Zetia, the first offspring of the Merck/Schering-Plough joint venture launched in 2002, and Vytorin a fixed-dose combination of Zetia and Merck's Zocor launched in 2004, have provided Schering-Plough a significant opportunity in the $23bn market for cholesterol-lowering drugs. Sales of Zetia already topped $1bn in 2004 while Vytron's market share continues to move forward, having captured over 7% of the US cholesterol market in its first year since launch. Although profits are split with partner Merck, Schering-Plough's share of the joint venture operating profit is expected to drive rapid earnings acceleration.

…Offset modest expectations elsewhere
Aside from Zetia and Vytorin, much of Schering-Plough's pharma portfolio suffered during the transition years 2002-2004. While most key franchises now appear back on track, only Remicade (ex-US only), Temodar and Nasonex are forecast to post double-digit sales growth through 2007. However, the in-licensing of Bayer's US primary care portfolio should leverage Schering-Plough's sales force. Looking ahead, the near term patent expiry profile of Schering-Plough appears fairly benign, but so are expectations for the pipeline which offers little of excitement aside from the 2005 launch of inhaled steroid Asmanex and the expected 2006 launch of anti-fungal treatment Noxafil.

Forecasts and ratios

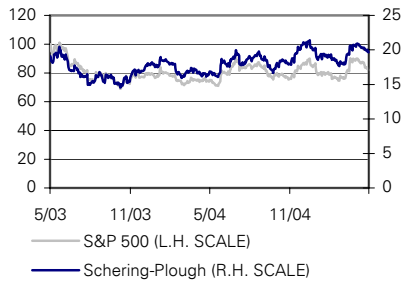
Year End Dec 31	2003A	2004A	2005E	2006E	2007E
Revenue (USDm)	8,334	8,272	9,505	10,169	10,753
DB PBT (USD m)	551	65	910	1,545	2,077
FY EPS (USD)	0.33	0.01	0.40	0.73	1.07
P/E (x)	53.0	1600.1	48.2	26.4	18.1
Dividend yield (%)	3.2	1.3	1.3	1.4	1.5

Source: Deutsche Bank

Buy

Price at 2 August 2005 (USD)	**20.96**
Price target	**24.00**
52-week range	**21.41-16.10**

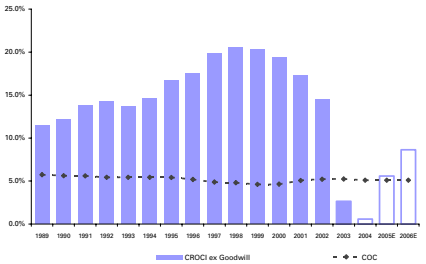
Price/price relative



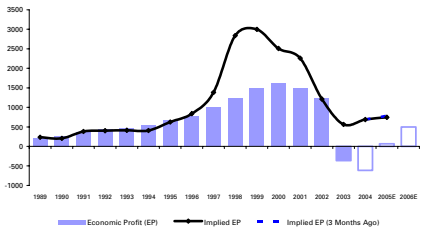
Stock data

Market cap (USD bn)	**28.7**
Shares outstanding	**1,451.0**
Free float (%)	**100**

Returns ex-Goodwill vs Cost of Capital



Economic/Discounted Economic Profit



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Figure 357: Key expiries and launches 2004-07E

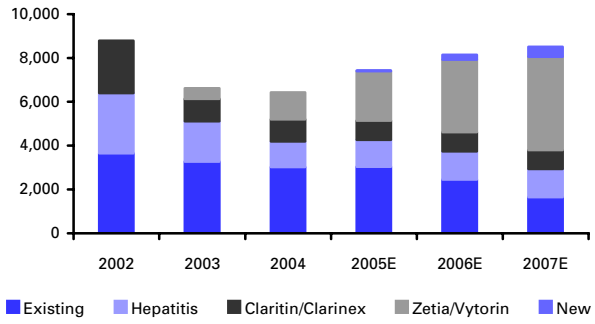
Patent expiries	2004 US Sales	% Pharma	Expiry date
Rebetol	$45m	1%	2004

New product	Peak sales	Indication	Launch date
Vytorin	>$2,000m	Cholesterol	2004
Noxafil	$500m	Fungal infections	2005
garenoxacin*	$300m	Bacterial infections	2006
SCH-D	$500m	HIV	2007

**US rights to be sublicensed*

Source: Deutsche Bank and Company information

Figure 358: Portfolio shift 2002-07E* ($m)



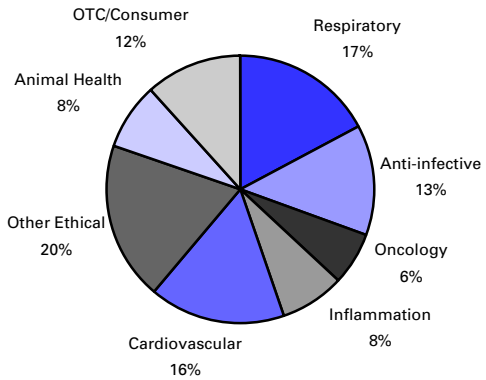
Source: Deutsche Bank and Company information **Zetia/Vytorin joint venture sales not consolidated*

Figure 359: Summary P&L ($m)

	2002	2003	2004E	2005E	2006E	2007E	CAGR
Sales	10,183	8,334	8,272	9,505	10,169	10,753	1.1%
Of which pharma	8,789	6,611	6,418	7,535	8,170	8,714	-0.2%
COGS	2,505	2,833	3,071	3,505	3,763	3,979	9.7%
SG&A	3,681	3,475	3,811	4,191	4,256	4,376	3.5%
R&D	1,425	1,468	1,527	1,619	1,550	1,570	2.0%
EBIT	2,572	558	(138)	191	600	828	-20.3%
EBITDA	2,944	975	316	686	1,135	1,388	-14.0%
EPS ($)	1.42	0.33	0.01	0.40	0.73	1.07	-5.6%
COGS %	*24.6%*	*34.0%*	*37.1%*	*36.9%*	*37.0%*	*37.0%*	*8.5%*
SG&A %	*36.1%*	*41.7%*	*46.1%*	*44.1%*	*41.9%*	*40.7%*	*2.4%*
R&D %	*14.0%*	*17.6%*	*18.5%*	*17.0%*	*15.2%*	*14.6%*	*0.9%*
EBIT %	*25.3%*	*6.7%*	*-1.7%*	*2.0%*	*5.9%*	*7.7%*	*-21.1%*

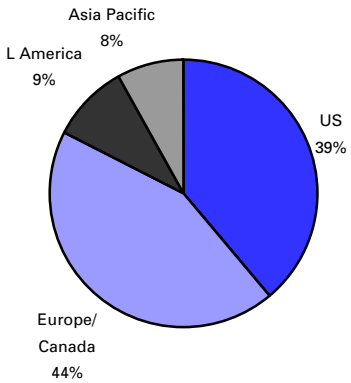
Source: Deutsche Bank and Company information

Figure 360: Group sales by category 2004*



Source: Company information **Includes Zetia/Vytorin sales joint venture sales*

Figure 361: Sales by geography 2004



Source: Company information

Figure 362: Key pharmaceutical products (sales in $m)

Brand	Generic	Lead Indication	Key US Patents	US exclusivity	Sales 2004	Sales 2007E
Respiratory						
Claritin	loratadine	Allergy	Expired	Expired	320	310
Claritin OTC (US)	loratadine	Allergy	Expired	Expired	419	450
Clarinex	desloratidine	Allergy	Expired	Jun-07	693	550
Nasonex	mometasone	Allergy	Jul-14	Expired	593	975
Asmanex	mometasone	Asthma	Jul-14	Mar-08	0	100
Anti-Infective						
Intron A	interferon	Hepatitis C	Biologic	Biologic	351	265
PEG-Intron	pegylated interferon	Hepatitis C	Biologic	Biologic	563	740
Rebetol	ribavirin	Hepatitis C	Expired	Expired	253	285
Avelox (US co-promo)	moxifloxacin	Antibiotic	Jun-09	Expired	44	250
Cipro (US co-promo)	ciprofloxacin	Antibiotic	Expired	Expired	43	180
Noxafil	posconazole	Anti-fungal	n.a.	n.a.	0	200
Cardiovascular						
Integrilin	eptifibatide	Thrombosis	Nov-14	May-03	325	310
Zetia (JV with MRK*)	ezetimibe	Cholesterol	Jun-15	Oct-07	1059	2200
Vytorin (JV with MRK*)	ezetimibe/simvastatin	Cholesterol	Jun-15	Oct-07	130	2400
Other						
Remicade	infliximab	Rheumatoid arthritis	Non-US	Non-US	747	1200
Temodar	temozolomide	Brain cancer	Nov-10	Aug-04	460	830
Caelyx	doxorubicin	Breast cancer	Non-US	Non-US	148	250

Source: Deutsche Bank and company information **Sales consolidated through JV. Share of profits reported as equity income*

NOTES

North America United States
Health Care Pharmaceuticals/Major

2 August 2005

Wyeth

Reuters: **WYE.N** Bloomberg: **WYE UN** Exchange: **NYSE** Ticker: **WYE.N**

Solid EPS with perceived low risk

Wyeth has core franchises in women's health, contraception, inflammatory diseases and vaccines. Although the vast majority of the company's revenues are generated from its ethical pharmaceutical business, Wyeth also derives around $1bn of sales from animal health (Fort Dodge) and $2.5bn from consumer health.

Performance of key brands to drive healthy earnings growth
We forecast Wyeth's key brands to drive upper single-digit sales and earnings growth through 2007. Although sales of Protonix and Effexor XR have begun to moderate in the face of increased competition and maturing markets, the resolution of capacity constraints and manufacturing backlogs should drive >50% growth for Enbrel and Prevnar in 2005. Peak sales of Enbrel (which is partnered with Amgen) should exceed more than $4 bn worldwide.

HRT sales stabilising post WHI study fallout
Premarin sales suffered a significant decline after a July 2002 WHI study linked hormone replacement therapy (specifically a high-dose version of Prempro) with an increased risk of breast cancer. Although the entire HRT market contracted as a result of the July 2002 study and others that followed, Wyeth's franchise has at last begun to stabilise with modest growth forecast going forward.

Fen/phen litigation resolving?
Wyeth's shares have also been plagued from snowballing litigation liabilities associated with the 1997 withdrawal of diet drugs fenfluramine and phentermine (known as fen/phen). Wyeth's litigation reserve now stands at a massive $21.1bn, but attempts to resolve many of the outstanding cases and cautious comments from the company suggest that final resolution may be possible over the next year.

Low generic threat, but pipeline still a couple years away
Wyeth faces limited patent risk in the coming years (aside from a patent challenge against $1.6bn Protonix), while the late-stage pipeline boasts a few compounds that could have blockbuster potential, namely DVVS-233, bifeprunox, and basedoxifne. However, the pipeline is largely a story for 2007 and beyond and may be overshadowed in the interim by concerns over slowing Rx trends for Wyeth's existing portfolio.

Forecasts and ratios

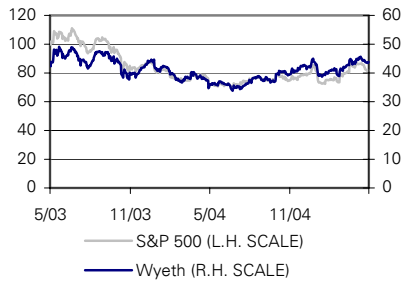
Year End Dec 31	2003A	2004A	2005E	2006E	2007E
Revenue (USDm)	15,850	17,358	19,075	20,432	21,930
DB PBT (USD m)	4,141	4,518	5,004	5,306	5,782
FY EPS (USD)	2.44	2.63	2.90	3.05	3.31
P/E (x)	17.1	14.7	15.3	14.5	13.4
Dividend yield (%)	2.2	2.4	2.1	2.3	2.3

Source: Deutsche Bank

Hold

Price at 2 August 2005 (USD)	**45.75**
Price target	**46.00**
52-week range	**45.60-33.80**

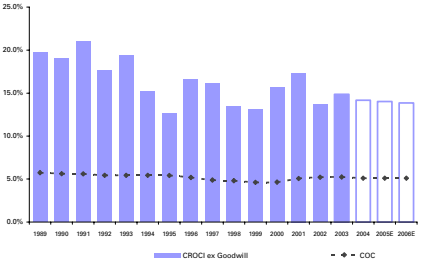
Price/price relative



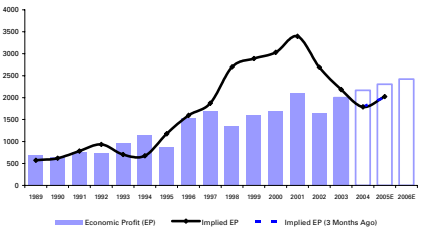
Stock data

Market cap (USD bn)	**60.9**
Shares outstanding	**1,319.8**
Free float (%)	**100**

Returns ex-Goodwill vs Cost of Capital



Economic/Discounted Economic Profit



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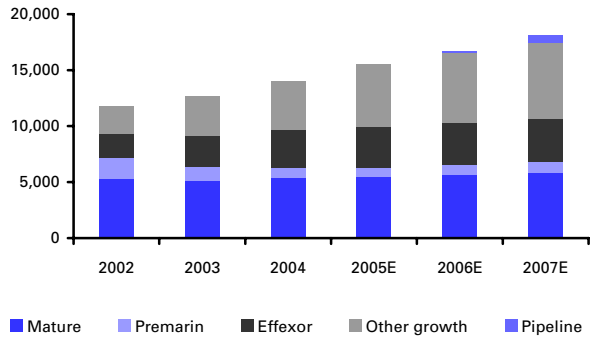
Figure 363: Key expiries and launches 2004-07E

Patent expiries	2004 US Sales	% Pharma	Expiry date
Zosyn	$395m	3%	2007

New product	Peak sales	Indication	Launch date
Tygacil	$500m	Bacterial infections	2005
Librel	$300m	Contraceptive	2006
bazedoxifene	$500m	Osteoporosis	2007
tanaproget	$300m	Contraceptive	2007
DVS-233	$1,000m	Depression	2007
bifeprunox	$500m	Schizophrenia	2007
temsirolimus	$300m	Cancer	2007

Source: Deutsche Bank and Company information

Figure 364: Portfolio shift 2002-07E ($m)



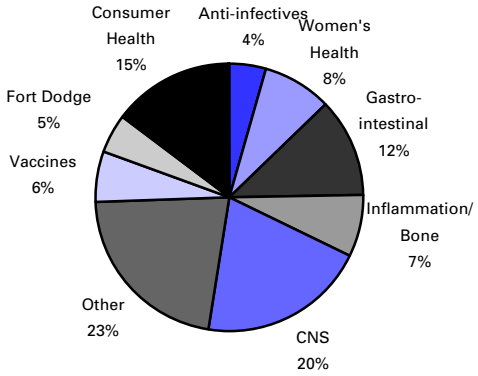
Source: Deutsche Bank and Company information

Figure 365: Summary P&L ($m)

	2002	2003	2004E	2005E	2006E	2007E	CAGR
Sales	14,584	15,850	17,358	19,075	20,432	21,930	8.5%
Of which pharma	11,733	12,621	13,964	15,594	16,872	18,260	9.2%
COGS	3,918	4,376	4,946	5,450	5,803	6,228	9.7%
SG&A	5,011	5,469	5,800	6,136	6,538	6,930	6.7%
R&D	2,080	2,093	2,315	2,675	2,900	3,100	8.3%
EBIT	3,575	3,912	4,298	4,814	5,191	5,672	9.7%
EBITDA	4,060	4,450	4,920	5,514	5,966	6,522	9.9%
EPS ($)	2.22	2.44	2.63	2.90	3.05	3.31	8.3%
COGS %	*26.9%*	*27.6%*	*28.5%*	*28.6%*	*28.4%*	*28.4%*	*1.1%*
SG&A %	*34.4%*	*34.5%*	*33.4%*	*32.2%*	*32.0%*	*31.6%*	*-1.7%*
R&D %	*14.3%*	*13.2%*	*13.3%*	*14.0%*	*14.2%*	*14.1%*	*-0.2%*
EBIT %	*24.5%*	*24.7%*	*24.8%*	*25.2%*	*25.4%*	*25.9%*	*1.1%*

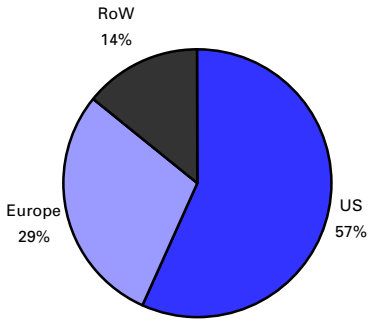
Source: Deutsche Bank and Company information

Figure 366: Group sales by category 2004



Source: Company information

Figure 367: Sales by geography 2004



Source: Company information

Figure 368: Key pharmaceutical products (sales in $m)

Brand Name	Generic Name	Lead Indication	Key US Patents	US exclusivity	Sales 2004	Sales 2007E
Gastrointestinal						
Protonix	pantoprazole	Ulcers/GERD	Jul-10	Feb-05	1591	1775
Zoton	lansoprazole	Ulcers/GERD	Non-US	Non-US	448	430
Contraception/HRT						
Premarin	n.a.	HRT	Expired	Expired	880	1015
Oral Contraceptives	n.a.	Contraception	Expired	Expired	590	568
Blood Products						
Benefix	Factor X	Haemophilia B	Biologic	Biologic	300	440
ReFacto	Factor VII	Haemophilia A	Biologic	Biologic	248	295
CNS						
Effexor XR	venlafaxine	Depression	Jun-08	Expired	3348	3950
n.a.	bifeprunox	Schizophrenia	n.a.	n.a.	0	95
DVS-233	n.a.	Depression	n.a.	n.a.	0	125
Anti-infective						
Zosyn/Tazocin	piperacillin	Antibiotic	Feb-07	Expired	760	1075
Prevnar	n.a.	Meningitis vaccine	Biologic	Biologic	1054	1800
Tygacil	tigecycline	Antibiotic	n.a.	n.a.	0	350
Anti-inflammatory						
Enbrel (co-promo)	etanercept	Rheumatoid arthritis	Biologic	Biologic	680	1550
Rapamune	sirolimus	Transplant	Sep-13	Expired	258	465
Indux	rhBMP-2	Bone fractures	Biologic	Biologic	165	300
n.a.	basodoxifene	Osteoporosis	n.a.	n.a.	0	95

Source: Company data, Deutsche Bank estimates

NOTES

Appendix

Abbreviated New Drug Application – The regulatory process whereby a generic manufacturer wishing to produce a copy of a patented drug can apply to have early physical, chemical and toxicological data and later clinically-derived safety and efficacy data for the original product taken "as read", thereby needing only to prove that its product is chemically the same as the original and is bioequivalent (behaves the same as the original drug in the patient).

Absorption – As part of the ADMET acronym for drug testing is how and to what degree animals/animal tissues incorporate a particular chemical compound in pre-clinical testing.

ACE Inhibitors - A class of compounds that block the action of Angiotensin Converting Enzyme thereby inhibiting the production of Angiotensin II, a potent blood vessel constrictor (vasoconstrictor). ACE inhibitors are often used as treatments for hypertension and congestive heart failure.

Acetylcholine – A chemical in the body which acts as a neurotransmitter, thereby propagating nerve impulses and causing cardiac inhibition, gastrointestinal peristalsis and other parasympathetic effects.

Acetylcholinesterase – An enzyme in the central nervous system which acts specifically to breakdown the neurotransmitter, acetylcholine.

Active Control – In a clinical trial when the drug under investigation is compared with an already tested, usually approved product rather than a non-active placebo (sugar tablet).

ADMET – An acronym used in drug testing standing for the absorption, distribution, metabolism, excretion and toxicology analyses that are undertaken in animals/animal tissues in order to characterise a pre-clinical developmental compound.

Advisory Committee – One of 17 different consulting panels of the Food and Drug Administration in the US, which often consider the merits of new products before marketing approval. Made up of expert scientists and physicians, these committees make recommendations on approvals and/or particular courses of action in therapeutic areas. Although not bound by Advisory Committee recommendations, the FDA usually follows their advice.

Agonist – A substance that has an affinity for a particular receptor and which interacts with it to initiate a response.

Aldosterone – A steroid hormone involved in the kidney's regulation of sodium (for which it facilitates re-absorption by the body in preference to potassium) and in the loss of hydrogen.

Allergen – A substance foreign to the body that elicits an immune response, also known as an allergic reaction.

Allergic Rhinitis – Inflammation of the nasal mucous membranes associated with an allergen, often plant pollens in hay fever.

Amino Acid – Organic acids in which one of the CH hydrogen atoms has been replaced with NH2. The twenty or so amino acids constitute the building blocks of proteins.

ANDA – See Abbreviated New Drug Application

Angina Pectoris – An acute severe chest pain, often radiating down the left arm, due to ischaemia (poor blood flow) of the heart muscle usually caused by coronary disease.

Angioplasty – A procedure to open narrowed arteries, usually via the introduction of a balloon tip catheter, which is then inflated to dilate the vessel.

Angiotensins – Compounds with profound blood vessel constricting (vasoconstrictive) activity, which are produced by the enzymatic action of renin on angiotensinogen.

Angiotensin I – A compound formed from angiotensinogen in an enzymatic reaction facilitated by renin. Further enzymatic action (via angiotensin-converting enzyme) forms angiotensin II, which produces constriction of the blood vessels.

Angiotensin II – A compound formed from Angiotensin I in a reaction mediated by angiotensin-converting enzyme. Angiotensin II significantly increases blood vessel constriction and therefore blood pressure. It is also the most powerful stimulus for the production and release of aldosterone.

Angiotensin Converting Enzyme – A compound that mediates the conversion of Angiotensin I, a relatively inert substance in the body, into Angiotensin II, a potent blood pressure-raising agent.

Angiotensin II Receptor Blockers – A class of compounds that interfere with the action of Angiotensin II, a potent blood pressure-raising agent, thereby producing a fall in blood pressure. Often used as a treatment for hypertension.

Angiotensinogen – A compound produced by the liver that is converted to angiotensin I by renin. It is involved in the renin-angiotensin system that regulates blood pressure levels.

Antagonist – A substance that has an affinity for a particular receptor and acts at it to inhibit the action of another agent which is also usually specific for that receptor.

Anti-aggregants – Drugs used to prevent the clumping of blood platelets. Such products have proved useful in the treatment of a number of cardiovascular conditions.

Antibody – Proteins produced by the body, which make up an important part of the immune system. They specifically target and destroy the foreign proteins (antigens) which usually provide the stimulus for their production.

Antigen - A protein that is foreign to the body and which provokes the production of neutralising antibodies by the immune system. These antibodies specifically target and destroy the antigen.

Antisense Technology – The use of single nucleotide chains which act as therapies by matching up and binding to specific mRNA molecules, thereby blocking the protein synthesis they would normally produce.

Apoptosis – The programmed cell death inherent to all normal cell types when the time is right. An apoptosis malfunction is possibly involved in the undifferentiated cell division seen in cancer tissue proliferation.

Apolipoprotein – Is the protein component of lipid and protein-containing lipoprotein complexes. These are a normal component of High, Low and Very Low Density Lipoproteins in Man**.**

Arterial – Pertaining to vessels carrying blood away from the heart.

As Treated – In a clinical trial, this analysis includes only those patients completing treatment. Those dropping out of the study are not included. This is not as robust an analysis as an "Intent To Treat" analysis, where all patients registered in the trial are included in the analysis.

Atherogenesis – The formation of atheroma or lipid (fatty) deposits, usually in artery walls. These are important in the pathogenesis (development) of arteriosclerosis.

Atherogenic – Having the ability to initiate, to increase or accelerate the process of atherogenesis.

Atheroma – Lipid (fatty) deposits in the walls of the arteries, producing a yellow swelling on the inner endothelial surface, characteristic of atherosclerosis.

Atherosclerosis – A nodular hardening of the arteries associated with the buildup of fatty deposits, the formation of fibrous tissue and calcification.

Baroreceptor - Receptors located in the vascular system and the heart sensitive to wall distension due to increased pressure. They form part of the reflex mechanism that tends to reduce that pressure.

Base Pairs – Couplings formed by the specific bonding of the nitrogenous bases adenine, thymine, cytosine and guanine, between complementary strands of DNA. Adenine binds with thymine and cytosine with guanine.

b.i.d. (or b.d.) – Of instructions written on a prescription, twice-daily.

Beta-Adrenergic Receptors – Cell surface proteins that bind to transmitters of the autonomic nervous system such as norepinephrine. Stimulus leads to the classic fight, flight or frolic response with an increase in heart rate, blood pressure and "readiness for action."

Beta cells – Those cells in the pancreas responsible for the secretion of insulin.

Beta-Blockers – A group of compounds that block the stimulus of beta-adrenergic receptors. Actions include a slowing of the force and rate of heart contractions. Often used in hypertension and anxiety.

Biotechnology – Is the use of cell chemistry to produce therapeutically useful proteins. Biotechnology seeks to industrialise and manipulate chemical reactions at the cellular level to produce significant quantities of often complex molecules.

Black Box Warning – In the US, a product can be launched or eventually issued with this severe warning that is included on its prescribing information. Such a warning usually refers to potentially life-threatening adverse effects.

Blockbuster – A product with annual sales in the order of $1bn is said to be a blockbuster.

Blood pressure – The pressure attained in the vessels of the body carrying the blood. Usually measured in millimetres of Mercury (mmHg) and expressed in two fractions, systolic, which relates to the pressure in blood vessels generated during contraction of the heart and diastolic, relating to the pressure in the same vessels when the heart is relaxed. Optimal readings are 120mmHg for systolic pressure and 90mmHg for diastolic pressure.

Body Mass Index – A measure of overweight/obesity also used as an indicator of likely complications due to excess weight. Calculated as an individual's weight in kilograms divided by the square of his/her height in metres.

Bronchospasm – The tightening of the smooth muscle of the lungs associated with an asthma attack.

Calcification – The hardening of artery walls associated with the buildup of non-soluble deposits of Calcium salts.

Calcium Channel Blockers – A class of compounds that act by inhibition of the passage of Calcium ions into muscle cells. They are often used as treatments for hypertension and angina.

Cardiac Output – A measure of the efficiency of the working of the heart usually expressed as the heart rate multiplied by the volume of contraction**.**

Cascade – Pertaining to a sequence of chemical reactions within the body.

Catabolism – Breaking down in the body of complex chemical compounds into simpler ones, often with the release of energy.

Catheter – A tubular instrument designed to allow passage of fluid from or into a body cavity. A balloon tip catheter is fitted with an inflatable tip, which can be used to facilitate passage of the tube through the blood vessel, to take haemodynamic (blood flow-related) measurements or to open a partially blocked blood vessel (angioplasty).

Cells – The smallest unit of living structure capable of independent existence, composed of a membrane-enclosed mass of protoplasm and containing a nucleus.

Central Nervous System – That portion of the nervous system comprising the brain and spinal column.

Central Pharmaceutical Affairs Council – An advisory body to Japan's Ministry of Health and Welfare, comprising 15 medical and pharmacological experts, which screens and evaluates data submitted for a new drug approval.

Cerebral Embolism – An obstruction of the vessels of the main parts of the brain, most often composed of a detached blood clot from a distant site, a mass of bacteria or other foreign body.

Chemotaxins – Are chemical substances that mediate the movement of cells or organisms.

Chiral – Denoting a chemical that can exist in a number of forms. A term usually used in relation to the different isomers of a particular compound. Isomers have identical chemical compositions but have atoms in differing positions within the molecule, thus conferring them with variable shapes potentially leading to differing chemical and physical properties.

Cholesterol – The most abundant steroid present in animal tissues, especially in bile and gall stones, and also present in food. It is important in the pathogenesis of atheroma formation in the arteries.

Chromosome – Packages of genetic information, in the form of DNA, located in the nucleus of cells. In humans 23 pairs of chromosomes contain an estimated 100,000 genes which code for specific proteins.

Clone – An individual organism or group of organisms derived from a single organism or cell and therefore having identical genetic make-up.

Codon – A triplet of nucleotides made from adenine, thymine, cytosine and guanine, which codes specifically for one of the twenty or so amino acids. The number and sequence of codons along a gene sequence determine the structure of the protein made by that gene.

Combinatorial Chemistry – The systematic, usually automated, synthesis of large numbers of similar, but distinct, chemical compounds in preparation for drug activity screening.

Committee on Proprietary Medicinal Products – Is an advisory committee to the European Medicines Evaluation Agency (EMEA), which assesses New Drug Applications.

Contractility – The ability of a substance, especially of muscle, of shortening, or becoming reduced in size, or developing increased tension.

Control Regions – Sequences within the non-protein coding junk DNA, which act to regulate gene expression and therefore protein synthesis.

Corticosteroids – Steroids produced by the tissue of the adrenal gland in the body.

CPMP – See Committee on Proprietary Medicinal Products.

Crossover – Of a clinical trial, when patient groups alternate between the various treatments and/or placebo during the course of the study.

Cytokines – Non-antibody proteins within the body, released by certain cells in response to specific antigens and which mediate the immune response.

Cytoplasm – The main constituent of a cell comprised of gel-like living matter, which contains various cellular structures and the nucleus.

Deep-Vein Thrombosis – A condition relating to the formation of blood clots, often in blood vessels of the lower limbs, following surgery or extended periods of immobilisation. These blood clots potentially block blood vessels locally or can detach and cause blockage elsewhere, for example in the lungs (Pulmonary embolism).

Diabetes – A metabolic disease in which carbohydrate utilisation is reduced and that of lipid and protein enhanced. It is caused by an absolute or relative deficiency of insulin and manifests as raised glucose levels in the blood. Long term complications include damage to nerves, the kidney and eyes.

Diastole – The resting or relaxation phase of the beating heart. The pressure in blood vessels during relaxation forms part of the measurement of blood pressure (see also systole and hypertension).

Distribution – As part of the ADMET acronym for drug testing is the distribution of a particular chemical throughout animals/animal tissues in pre-clinical testing.

Diuresis – Usually denotes the excretion of unusually large volumes of urine.

Diuretic – Is an agent that promotes the production of urine.

DNA – Deoxyribonucleic Acid. A strand of molecules containing genetic instructions made up of linked and repeating sub-units called nucleotides, based on the nitrogenous bases adenine (A), thymine (T), cytosine (C) or guanine (G). Each of these bases pairs with another on a complementary strand of DNA (A with T and C with G) to form a double helix.

Double Blind – In a clinical trial when neither the patient nor the investigating physician is aware what has been administered, be it active treatment or placebo.

Drug Label – The prescribing instructions and other product information agreed with the Food and Drug Administration, which is routinely included in the packaging of a drug product.

Embolism – An obstruction of vessels, usually blood vessels, most often composed of detached blood clot from a distant site, a mass of bacteria or other foreign body.

EMEA – See European Medicines Evaluation Agency

Enantiomer – One of a pair of molecules that are mirror images of each other.

Endothelial cells – Flat cells that typically line the walls of blood cells and the heart. The lining of a layer of such cells is known as endothelium.

Enzyme – A protein secreted by cells, which acts as a promoter or catalyst of chemical reactions in the body apparently remaining unchanged by the reaction itself.

Eosinophils – A form of white blood cell also known as a leukocyte.

Essential Hypertension – Blood pressure that is raised above normal but with no discernible cause. Also known as idiopathic hypertension.

European Medicines Evaluation Agency. – The European Union's drug regulatory agency which oversees all aspects of pharmaceutical regulation, from clinical trials and registration, through to manufacturing standards and promotional claims.

Excretion – As part of the ADMET acronym for drug testing is the method by which animals/animal tissues rids itself of a particular chemical compound and its breakdown products in pre-clinical testing.

Exogenous – Something originating or that is produced outside an organism.

FDA – See Food & Drug Administration

Fee-For-Service – The most flexible of Managed Care plans where individuals simply choose the physician they wish to see and receive the treatment considered most suitable by that doctor.

FEV1 – Forced Expiratory Volume of air expelled from the lungs in one second. A frequently used test of lung function.

Fibrin – An elastic filamentous protein derived from fibrinogen via the action of thrombin. It is a component of blood clots.

Fibrinolysis – The breakdown of fibrin by a chemical reaction known as hydrolysis. In therapeutic terms, this is carried out with products known as fibrinolytics.

Food & Drug Administration – The US government's regulatory agency which oversees all aspects of pharmaceutical regulation, from clinical trials and registration, through to manufacturing standards and promotional claims.

Formulary – A group of pharmaceuticals approved for use by a particular institution.

Gastrin – A hormone secreted in the mammalian stomach which stimulates the secretion of hydrochloric acid by the parietal cells of the gastric glands.

Gene – A specific sequence of nucleotides, or DNA sub-units, that direct protein synthesis.

Gene Expression – Refers to whether a gene is 'turned on' or activated to direct protein synthesis. Specific control regions within junk DNA regulate gene expression.

Generic – Is the basic chemical constituent of a pharmaceutical product.

Genome – The blueprint of genetic information of an organism often referred to in humans as the "book of life." The Human Genome, which was finally sequenced in June 2000, comprises some 3.1bn base pairs of information, only 10% of which are thought to code for proteins, arranged on 23 pairs of chromosomes.

Genomics – The study of all aspects of the Genome, the blueprint of genetic information, particularly its structure and function, as it relates to humans.

Genotype – The genetic constitution of an individual, sometimes used with respect to the make-up of a group of individuals with similar characteristics as determined by one gene.

GERD – Gastro-Esophageal Reflux Disease, a condition in which acid is regurgitated from the stomach into the esophagus causing heartburn pain and in more severe chronic cases, tissue erosion. Acid secretion suppressants such as H2-blockers and proton pump inhibitors are used to treat the condition.

Glitazones – A class of chemicals also known as the thiazolidinediones, which are sensitisers of body tissue to insulin and are, therefore, used as treatments for diabetes. Examples include Actos (Takeda/Lilly), Avandia (GlaxoSmithKline) and the now withdrawn Rezulin (Pfizer).

Glucagon – A hormone involved in glucose metabolism. It promotes the elevation of blood glucose levels by the breakdown of glycogen in the liver. Sometimes used to treat hypoglycaemic coma induced by exogenously administered insulin.

Glucocorticoids – Any steroid-like compound capable of significantly influencing intermediary metabolism and of exerting a clinically useful anti-inflammatory effect.

Glucogenic – Giving rise to the production of glucose in the body.

Glycosylated haemoglobin – Any one of the four haemoglobin A fractions (Ala1, Ala2, Alb and Alc) to which glucose and related monosaccharides bind. Concentrations are raised in

the red blood cells of patients with Diabetes Mellitus, and can be used as a retrospective measure of glucose control over time in such patients.

H2 Antagonists – A class of compounds that inhibit the action of histamine receptors in the stomach, reducing gastric acid secretions. As such, they are useful in the treatment of GERD and ulcer disease.

Haemoglobin – A respiratory protein found in red blood cells responsible for the oxygen carrying capacity of the blood.

Haemodynamic – Pertaining to the movement of blood.

Haemorrhagic stroke – A condition in which bleeding into the tissues of the brain causes damage.

Health Maintenance Organisation – Part of the managed care system, these groups administer the drug benefit of individuals, usually on behalf of their employer. The pooling of large numbers of people in HMO schemes allows bulk purchasing and the negotiation of discounts. These organisations range from relatively inflexible Staff Model HMOs, which employ physicians and use strict formularies to control drug availability, through to Group or Network HMOs where the physician is contracted to one, or a number of HMOs, respectively. Inevitably, less influence can be exerted on physicians' prescribing decisions in these more loosely structured entities.

HDL-cholesterol – High-density lipoprotein cholesterol is one of a number of lipid-protein complexes present in the body. Also colloquially known as "good" cholesterol because of the beneficial effect it has on the evolution of cardiovascular disease.

High Throughput Screening – The systematic, usually automated rapid screening of compounds through a wide range of assays to determine their biological activity.

Histamine – Is a compound that is a powerful stimulant of gastric secretions, of smooth muscle constriction and is a vasodilator of both capillaries and arterioles. Its inhibition is therefore useful in the treatment of a number of conditions including GERD, ulcer disease and asthma.

HMG Co-A reductase – 3-hydroxy-3-methylglutaryl coenzyme A reductase is the rate-limiting enzyme in the intracellular synthesis of cholesterol. Its action is inhibited by the statins which are the most frequently used compounds for cholesterol reduction.

HMO – see Health Maintenance Organisation.

Hormone – A chemical substance formed in one organ or part of the body which then exerts its effect elsewhere within the body.

Hydrolysis – A chemical process whereby a compound is cleaved into two or more simpler compounds with the uptake of water. It is effected by the action of acids, alkalis, or enzymes.

Hyperglycaemia – An excess of glucose in the circulating blood, especially with reference to fasting levels.

Hypertension – A condition in which blood pressure is raised above the normal range as measured in millimetres of Mercury (mmHg). Blood pressure is expressed in two fractions. Systolic, which relates to the pressure in blood vessels generated during contraction of the heart and diastolic, which relates to the pressure in those vessels when the heart is relaxed.

Treatment to reduce hypertension is usually considered appropriate once systolic pressure exceeds 140mmHg and/or diastolic pressure exceeds 90mmHg.

Hypoglycaemia – An abnormal depletion of circulating blood glucose levels sometimes engendered by overdose of diabetes treatments such as insulin.

Hypolipidaemics – Products that reduce lipid levels in the blood.

Hypotension – A blood pressure that is lower than the normal range as measured in millimetres of Mercury (mmHg). Blood pressure is expressed in two fractions. Systolic, which relates to the pressure in blood vessels generated during contraction of the heart and diastolic, which relates to the pressure in the same vessels when the heart is relaxed. Optimal blood pressure is regarded as 120mmHg diastolic and 80mmHg systolic.

Incidence – The number of new cases of a disease in a defined population over a specific period of time.

IND – see Investigational New Drug.

Independent Physician Association – A loosely based collection of physicians in an organisation that is part of the Managed Care system. The range of suggested formularies they employ allows negotiated discounts for bulk drug purchases to be obtained but in reality IPAs exert little influence on physicians' prescribing habits.

Inflammation – Is the term for the collective changes that occur in tissues in response to injury and which eventually lead to healing. These changes principally, but not always, involve redness, warmth, swelling and pain.

Inotrope – Is a compound that affects the contractility of muscular tissue. Usually relates to the use of positive inotropes in heart failure.

In silico – Pertaining to experiments or reactions occurring on a silicon chip. Relates particularly to recent advances in experimental biology.

Insulin – A peptide hormone secreted by beta cells in the pancreas that promotes glucose utilisation, protein synthesis and neutral lipid storage. It is used in an injectable formulation for the treatment of diabetes mellitus.

Intent to Treat – In a clinical trial this analysis includes all patients originally registered, even if they subsequently withdrew from the study. This is a more robust analysis than "as treated" where only those patients completing treatment are included.

Intracellular – Occurring within the cell.

Investigational New Drug (IND) – A drug candidate for which the sponsor company has permission from the regulatory authorities, usually the US Food and Drug Administration, to test a particular compound in clinical trials.

In vitro – Pertaining to experiments or reactions occurring in the artificial environment that is the laboratory test-tube. Literally meaning "in glass."

In vivo – Pertaining to experiments or reactions occurring within a living organism.

Ions – An atom or group of atoms carrying an electric charge.

IPA – See Independent Physician Association.

Ischaemia – A reduction in blood flow to tissues usually as a result of blood vessel blockage.

Ischaemic Stroke – A condition in which blood vessel blockage leads to brain tissue damage.

Isomers – The different forms in which certain compounds can exist. Isomers have identical chemical compositions but have atoms in differing positions within the molecule thus conferring them with variable shapes potentially leading to differing chemical and physical properties.

Junk DNA – Regions of DNA strands that have no known coding properties for protein synthesis. Of the 3.1bn base pairs of genetic information only 10% is thought actively to code for protein synthesis. Within the remainder, sequences of DNA act as control regions to regulate gene expression.

LDL-Cholesterol – Low-density lipoprotein cholesterol is one of a number of lipid-protein complexes present in the body. Also colloquially known as "bad" cholesterol because of the detrimental effect it has on the evolution of cardiovascular disease.

Leukotrienes – Products of Arachidonic acid metabolism thought to be involved as mediators of inflammation and with a role in the allergic response.

Lipids – Substances extracted from animal or vegetable cells that are fat-soluble.

Lipoproteins – Are compounds or complexes within the body which contain both lipids and proteins.

Lumen – Is the space forming the interior of a tubular structure such as a blood vessel or the intestine.

Lymphocyte – A form of white blood cell formed in the lymphatic tissue (e.g. lymph nodes, spleen. Thymus, tonsils etc) throughout the body.

Macrophages – Are usually large, long-lived cells widely distributed throughout the body, which are actively involved in the body's defence against disease. They actively engulf and destroy invading bacterial and inert substances and are involved in the production of antibodies and cell-mediated immune response.

Managed Care – Is a concept employed in the US, which involves appointing specific providers to the task of managing actively the provision of healthcare for a group of individuals. For example, this involves Health Maintenance Organisations, which administer the drug benefit of individuals, usually on behalf of their employer. The pooling of large numbers of people in HMO schemes allows bulk purchasing and the negotiation of discounts. These organisations range from relatively inflexible Staff Model HMOs, which employ physicians and use strict formularies to control drug availability, through to Group or Network HMOs where the physician is contracted to one, or a number of HMOs, respectively. Inevitably, less influence can be exerted on physicians' prescribing decisions in these more loosely structured entities.

Markers – Surrogate endpoints, the measurement of which is often used in clinical trials to demonstrate a response to treatment. Typically, this could involve blood-borne entities such as copies of a virus (viral load in HIV trials) or proteins indicative of tumour activity in cancer trials.

Mast Cells – A connective tissue cell that is believed to contain substances, which are mediators of the allergic response such as histamine. Stabilisation of such cell with Intal is used as an asthma treatment.

Medicaid – A US scheme funded by State and Federal government designed to provide the cost of hospitalisation, doctors' visits and prescription drugs for those individuals with low incomes.

Medicare – The US nationwide federally funded healthcare programme for the elderly and disabled.

Membrane – Is a covering or skin for cells, tissues or organs within the body.

Messenger Ribonucleic Acid – A molecule transcribed in the cell nucleus using unwound DNA as a template. It is almost the same as the original DNA with the exception that another nucleotide, uracil, takes the place of thymine. The mRNA molecule then moves out of the nucleus into the surrounding cellular fluid, or cytoplasm, where it attaches to a ribosome to be read (translated) producing a protein.

Metabolism – As part of the ADMET acronym for drug testing is the way animals/animal tissues break down a particular compound in pre-clinical testing.

Metastasis – The shifting of a disease, or its local manifestations, from one part of the body to another, as in the development of new cancerous growths remote from the site of the primary tumour.

MHLW – see The Ministry of Health, Labour and Welfare.

Ministry of Health, Labour and Welfare – The Japanese government's drug regulatory agency which oversees all aspects of pharmaceutical regulation, from clinical trials and registration, through to manufacturing standards and promotional claims.

Molecular Imaging – A technique used in drug development that provides information on the shape and configuration of a substance under investigation.

Monoclonal (Antibody) – A specific antibody produced from a clone or genetically identical population of hybrid cells.

Mononuclear – Having only one nucleus. Used especially in reference to blood cells.

Monosaccharides – Are carbohydrates that cannot form any simpler sugars by simple hydrolysis.

Monotherapy – Is the treatment of a condition with only one product.

mRNA – see Messenger Ribonucleic Acid.

Mucosa – The mucous lining of various tubular structures within the body, consisting of epithelium, lamina propria (a layer of connective tissue) and, in the digestive tract, a layer of smooth muscle.

Mucus – A clear viscid secretion of the mucus membranes, consisting of mucin, epithelial cells, leukocytes and various inorganic salts suspended in water.

Myocardial infarction – Heart attack, as in infarction or death of heart tissue (myocardium) brought about by a sudden loss of blood supply.

National Institute for Clinical Excellence – A UK government advisory body which considers the cost effectiveness of new products.

NDA – See New Drug Application.

Neurotransmitter – Any specific substance released by a nerve cell on stimulation, which crosses the Synapse (nerve gap) which divides nerve cells, to stimulate or inhibit the post-synaptic nerve cell.

New Chemical Entity – As the name implies, a newly synthesised compound for which a sponsor company will likely undertake drug development.

New Drug Application (NDA) – The filing made to the regulatory authorities, usually the Food and Drug Administration, by a drug sponsor for the approval of a product once clinical testing has been completed.

NICE – See National Institute for Clinical Excellence.

Nitrogenous Bases – Adenine, thymine, cytosine and guanine are the four molecules that bind following specific rules (adenine with thymine, cytosine with guanine) and are the basic building blocks of DNA.

NSAIDs – Non-steroidal anti-Inflammatory drugs. A group of drugs used for the treatment of pain and inflammation associated with a number of conditions such as arthritis.

Nucleotides – Linked and repeating sub-units of DNA strands which are based on the four nitrogenous bases adenine, thymine, cytosine and guanine.

Nucleus – The central, typically rounded structure of the plant or animal cell containing the genetic information.

Obese – An overweight person with a calculated body mass index (BMI) of 30 or higher. BMI is an indicator of likely complications due to excess weight. Calculated as an individual's weight in kilograms divided by the square of his/her height in metres.

o.d. – Of instructions on a prescription meaning once daily.

Oedema – The buildup of fluid in body cells, tissues or cavities.

Oesophagus – Is that portion of the digestive canal between the throat region, or pharynx and the stomach.

Open Trial – A clinical trial where both the patient and investigating physician are aware what has been administered, be it active treatment or placebo.

Orange Book – The US Food and Drug Administration's list of patents recognised on approved branded products.

Orphan Drug – A drug recognised by the regulatory authorities (different conditions apply in different geographies) as being useful for a relatively rare condition affecting only a limited number of patients. Orphan Drug status affords certain assistance to the drug sponsor (R&D grants, favourable tax treatment, etc) and a period of market exclusivity for the product.

Overweight – A person with a calculated Body Mass Index (BMI) in a range of 25 to 29.9. BMI is an indicator of likely complications due to excess weight. Calculated as an individual's weight in kilograms divided by the square of his/her height in metres.

Oxidise – A reaction in which a compound is combined with oxygen or loses electrons.

P-value – A statistical term measuring whether a trial outcome is statistically significant. In biological systems a p-value of lower than 0.05 is deemed to be significant.

Parasite – Is an organism that lives in or on another and derives nourishment therefrom.

Patent – Is the legally granted protection, usually 20 years, for scientific innovation, given to a company that has discovered a new molecule or novel scientific process.

Pepsin – Is the principal digestive enzyme of gastric juice, formed from pepsinogen.

Pepsinogen – A proenzyme formed and secreted by the chief cells of the gastric mucosa which is acted upon by gastric juices and pepsin itself to form active pepsin.

Peptide – A compound containing two or more amino acids combined together in the same molecule.

Peristalsis - A rhythmic wave of contractions and relaxation alternating along the length of the intestine or other tubular structure which propel internal contents along its length.

Peroxisome proliferator-activated receptor (PPAR) agonists – Are groups of compounds which stimulate PPA receptors. They are variously under investigation for the treatment of diabetes.

Pharmacogenetics – Is the genetic basis for variation in drug response.

Pharmacogenomics – A group of related technologies concerned with understanding the genetic basis of a drug response.

Pharmacokinetics – The movement of drugs within biological systems as affected by their uptake and distribution through the body, binding to receptors and tissues, elimination from the body and the effect the body has on the drug.

Pharmacology – The science concerned with drugs, their sources, appearance, chemistry, actions and uses.

Pharmacopoeia – A collection of drug product descriptions, or monographs, which depict their characteristics and the properties and standards for the strength and purity of those compounds.

PhRMA – Pharmaceutical Research & Manufacturers of America is the leading trade association of the Ethical Pharmaceutical industry in the US.

Phospholipids – Are lipids (fatty substances) containing phosphorus.

Placebo – The non-active reference material (often referred to as a 'sugar pill') used in clinical trials designed to determine the relative efficacy of a drug candidate.

Plasma – Is the liquid portion of the blood.

Plasmin – Is an enzyme (aka. Fibrinolysin), that converts fibrin to soluble products. It occurs in plasma as plasminogen and is activated to plasmin by organic solvents and certain therapeutics.

Platelet – An irregularly shaped structure found in the peripheral blood containing granules and cytoplasm but with no definite nucleus, which is involved in the blood clotting process.

Point of Service – A healthcare plan under which individuals can consult one of a number of physicians recommended by the plan manager. This physician will then be responsible for the basic healthcare needs of the patient but can refer to a specialist should the need arise. However, referral can lead to further out-of-pocket expense for the patient.

Polymorphisms – Literally "many forms" is used in the context of DNA analysis to highlight the small variations that produce diversity between individuals.

Polysaccharides – A carbohydrate containing a large number of saccharide (sugar) groups.

PPO – See Preferred Provider Organisation.

Preferred Provider Organisation – A healthcare plan under which patients can elect to consult one of a number of physicians recommended by the PPO manager. The physician provides a discount on usual fees in return for regular referrals from the PPO. Patients can consult a non-plan physician for an additional out-of-pocket expense.

Prevalence – Is the number of cases of a disease existing in a given population at a particular moment in time.

Primary End-Point – In a clinical trial, this is the most important pre-determined objective of the study.

Priority review – Is an accelerated review period for a New Drug Application within the Food and Drug Administration's user fee system. This six-month review is shorter than the standard 12-months.

Prophylactics – Are drugs used to prevent a disease or a process that can lead to disease.

Proteins – Are large molecules consisting of chains of the 20 alpha amino acids. They comprise three-quarters of the dry weight of most cell matter and are involved in structures, hormones, enzymes, muscle contraction, immunological response and essential life functions.

Proteomics – The study of proteins in terms of their synthesis, structure and function.

Proton Pump – The mechanism by which Hydrogen ions are released into the stomach, thereby forming an acid environment to facilitate the digestion of food.

Protoplasm – The living matter that comprises the inside of cells, be they animal or vegetable, in which the nucleus is suspended.

Pulmonary Embolism - An obstruction of the pulmonary arteries of the lung, most often composed of detached blood clot from a distant site following an operation or confinement to bed.

QT prolongation – Is a side effect noted with a number of pharmaceuticals and involves a distortion of the normal conduction of electrical impulses across the heart, which manifests as an extension of the time between two points (Q and T) on an electrocardiograph.

Radioisotope – Is a radioactive version of an element, which gradually loses its larger number of neutrons via the emission of radiation. Radioisotopes are often used in the localised treatment of tumours.

Randomised – In a clinical trial, when patients are equally likely to be assigned to the active drug versus placebo arm regardless of disease or demographic characteristics.

Rational Drug Design – The systematic design of new drug candidates using molecular modeling and a detailed knowledge of the properties of various chemical compounds.

Racemic – Is the name given to an optically inactive mixture of two or more separable isomers.

Receptor – Is a structural protein on the cell surface or within the cytoplasm of a cell that binds to a specific factor, such as a hormone, antigen or neurotransmitter.

Recombinant – A microbe, or strain, that has received chromosomal parts from different parental strains. Often used to denote the insertion of a sequence of DNA, by chemical or biological means, into the DNA of a recipient organism with the objective of producing therapeutically useful products.

Renin – Is an enzyme that converts angiotensinogen to angiotensin and, part of the renin-angiotensin-aldosterone system is involved in the regulation of blood pressure.

Ribosome – A structure in the cytoplasm of a cell which facilitates the reading (translation) of a strand of mRNA into a protein by the specific selection and adding together of a chain of amino acids.

Seasonal Allergic Rhinitis – An inflammation of the nasal mucous membranes associated with plant pollen as allergens. Also known as in hay fever.

Secondary End-Point – In a clinical trial pre-determined objectives for analysis but deemed to be less important than the Primary end-point.

Secretagogue – Is an agent that promotes secretion.

Single Blind – In a clinical trial where the physician but not the patient is aware what has been administered be it active treatment or placebo.

sNDA – See Supplementary New Drug Application.

SNPs – Single nucleotide polymorphisms are minor changes in the make up of DNA that account for the variation seen between individuals.

Spasmogens – A substance, usually released by the body in response to stimulus, which causes spasms in smooth muscle. In the lungs this leads to contraction of the airways, the so-called asthma attack.

Statins – A colloquial collective name for the HMG Co-enzyme A reductase inhibitors, which are frequently used to reduce cholesterol levels.

Supplementary New Drug Application – Is the regulatory process whereby a new indication or formulation for use in the USA is filed with the Food and Drug Administration.

Synapse – The functional membrane to membrane contact of a nerve cell with another nerve cell, an effector (muscle or gland) cell, or a sensory receptor cell. The synapse subserves the transmission of nerve impulses, usually via the release of a neurotransmitter into the synaptic cleft (or gap) which then exerts an effect on cells on the other side of the cleft.

Systemic – Pertains to an action within the body and usually refers to the action of a pharmaceutical.

Systole – The contracting phase of the beating heart. The pressure in blood vessels produced by such contraction forms part of the measurement of blood pressure (see also diastole and hypertension).

T-cells – A long-lived cell of the immune system also known as a T lymphocyte, which is responsible for the cell mediated immunity.

Thrombosis – The formation or presence of a blood clot (thrombus) within blood vessels, which may cause infarction (death) of the tissues supplied by that vessel.

t.i.d. – Of instructions written on a prescription, three times a day.

Total Peripheral Resistance – That resistance to the passage of blood around the body afforded by small blood vessels of the vascular system.

Toxicology – As part of the ADMET acronym for drug testing is the toxicity profile demonstrated in animals/animal tissues by a particular compound in pre-clinical testing.

Toxin – Is a substance that is poisonous to the organism.

Transcription – The process whereby mRNA is produced by the binding of nucleotides in the nucleus of a cell using unwound DNA as a template. The mRNA produced is almost the same as the original DNA with the exception that that a fifth nucleotide, uracil, takes the place of thymine.

Transgenic – An animal that has been produced from a cell cloned after genetic alteration to carry genes, usually human, that will allow the production of therapeutically useful (human) proteins

Translation – The process whereby the mRNA molecule produced by the binding of nucleotides during transcription moves out of the nucleus of the cell into the surrounding cellular fluid, or cytoplasm. There it attaches to a ribosome and is read, or translated. This process selects and adds together specific amino acids thereby producing a protein.

Unblinded Trial – A clinical trial where both the patient and investigating physician are aware what has been administered, be it active treatment or placebo.

User Fee (Deadline) – A sum of money (currently circa $300,000) which a company sponsoring a New Drug Application in the US pays to the Food and Drug Administration for review of the product. In return the FDA agrees to render a decision on the application within 12-months for a standard review and within six-months (priority review) for a product which represents a significant advance on existing therapies.

Vasculature – Is the vascular (blood vessel) network of an organ.

Vasoconstriction – Is the narrowing of the blood vessels, usually leading to an increase in blood pressure.

Vasodilation – Is the relaxation of the blood vessels, usually leading to a decrease in blood pressure.

Vasopressor – An agent producing vasoconstriction (contraction of the blood vessels) and an increase in blood pressure, usually understood to be systemic arterial pressure, unless otherwise specified.

Ventricles – Are the lower chamber of the heart.

VLDL-cholesterol – Very Low-density lipoprotein cholesterol is one of a number of lipid-protein complexes present in the body. It has a detrimental effect on the evolution of cardiovascular disease although not as pronounced as LDL-cholesterol.

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Appendix 1

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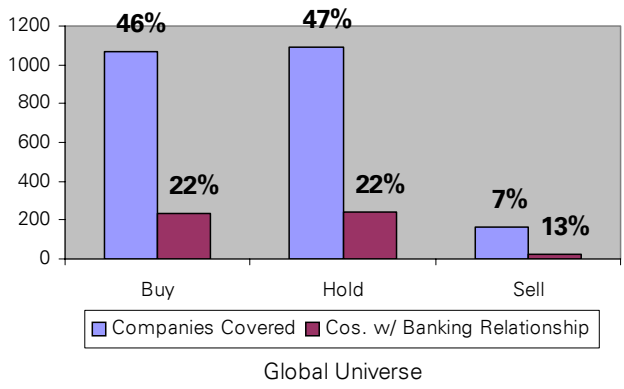
Equity rating key	Equity rating dispersion and banking relationships

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